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Emerging Data and Best Practices for the Use of Novel Therapies in Endometrial Cancer: Managed Care Considerations in an Evolving Treatment Paradigm

Best Practices in the Treatment and Management of Acute Myeloid Leukemia: Managed Care Decision-Making in an Evolving Landscape

Incorporating the Latest Treatment Changes in Prostate Cancer: Applying the Latest Evidence to Improve Outcomes

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Emerging Data and Best Practices for the Use of Novel Therapies in Endometrial Cancer: Managed Care Considerations in an Evolving Treatment Paradigm

Shannon N. Westin, MD, MPH

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For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

The treatment of advanced endometrial cancer has significantly improved over the last few years with studies showing improved survival. The treatment of this cancer is now becoming biomarker-directed and includes triple therapy for many patients.

Key Points

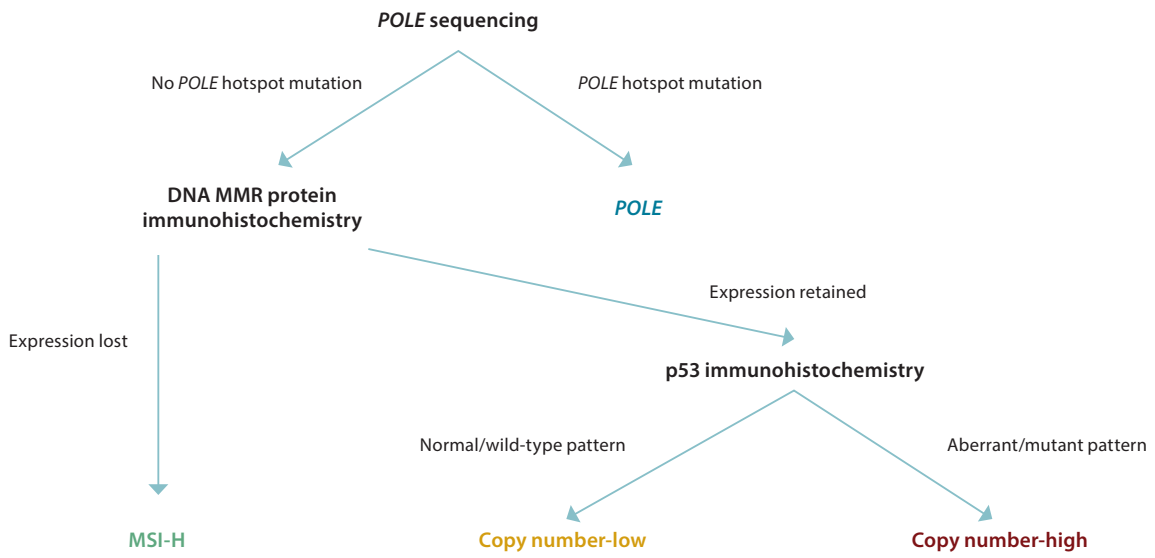
- Endometrial cancer incidence is increasing, and disparities exist in survival based on race/ethnicity.
- Movement toward biomarker-directed therapy in endometrial cancer is improving outcomes for patients.
- The standard of care for first-line treatment of metastatic/recurrent disease recently changed significantly.
- Toxicity management to maximize value-based care is essential.

ENDOMETRIAL CANCER IS THE MOST common gynecologic cancer and unlike other solid tumors, its incidence is growing. In 2023 an estimated 66,200 cases of uterine cancer will occur in the United States (U.S.) and 13,030 women will die from this cancer.[1] These estimates include both endometrial cancers and uterine sarcomas. Up to 10 percent of uterine cancers are sarcomas, so the actual numbers for endometrial cancer cases and deaths are slightly lower than these estimates. Endometrial cancer is the fourth most common cancer in women and the sixth cause of cancer deaths. It is more common than ovarian and cervical cancer and the mortality with endometrial cancer is approaching that of ovarian cancer.

Endometrial cancer affects mostly post-menopausal women.[2] The average age of women diagnosed with endometrial cancer is 60 years and it is uncommon in women under the age of 45 years. Today there are more than 600,000 survivors of endometrial cancer in the U.S. A woman's overall lifetime risk is 3.1 percent.[3]

The overall five-year survival rate for endometrial cancer is 81 percent.[3] Like all cancers, when diagnosed early, chances of survival are better. For endometrial cancer, 66.7 percent are diagnosed at the local stage which can be cured with surgery with or without radiotherapy. The five-year relative survival for localized uterine cancer is 94.9 percent which is in sharp contrast to the rate for metastatic

Exhibit 1: Principles of Molecular Analysis[8]



disease which is 20 percent.

The incidence of endometrial cancer is increasing in the U.S. but this increase is largely driven by ethnicity.[4] Women of color – Black, Latinx – have an increasing incidence and mortality. Racial disparities in endometrial cancer survival are predominantly attributable to increased advanced stage due to delay in diagnosis, high-grade and aggressive histologic subtype tumors, and differential use of surgery in Black women.[5] Distrust of the medical system, not reporting post-menopausal bleeding, lack of insurance or low-income status, provider poor adherence to guideline-based care, and institutional biases also contribute. Black patients are more likely to receive quality care at high-volume treatment centers, which have been associated with decreased racial disparity, fewer surgery complications, and improved outcomes.[6,7]

The National Comprehensive Cancer Network (NCCN) provides guidelines on managing endometrial cancer.[8] The primary treatment of early-endometrial cancer is surgery with or without adjuvant chemotherapy and/or radiation. Major advances in therapy have been made in treating metastatic/recurrent stage disease.

Treatment of endometrial cancer has been moving away from treating everyone the same to tumor specific molecular-based treatment. Tumors can be classified into four main groups based on molecular testing – p53 mutation, no specific molecular profile (NSMP), microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR), and POLE.[8-10] POLE is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair. POLE positivity indicates a good prognosis, MSI-H/dMMR has an intermediate prognosis, NSMP has a variable prognosis somewhere between good and intermediate, and p53 has a poor prognosis.[11,12] The molecular subgroups respond to therapy differently and therefore may require escalation or de-escalation of therapy compared to previous NCCN guidelines.[8]

Tumors with many mutations like MSI-H/dMMR and POLE ("hot" tumors) respond better to immunotherapy than tumors with few mutations ("cold" tumors). There are combination therapy strategies which can turn cold tumors into hot tumors so they respond to immunotherapy – these are discussed later.

Molecular testing is now recommended in the NCCN Guidelines to complement morphologic assessment regardless of histologic tumor type.[8] Getting testing before treatment is important for making treatment decisions. As shown in Exhibit 1, testing begins with POLE. If POLE is positive, testing can stop. These patients have such a good prognosis that they may be able to receive de-escalated therapy. Studies are ongoing to determine if those with POLE positive can be treated with just a hysterectomy and no adjuvant chemotherapy or radiation. Those with

Exhibit 2: NCCN First-Line Therapy for Metastatic/Recurrent Disease[8]

Preferred
• Carboplatin/paclitaxel (category 1 for carcinosarcoma)
• Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma, category 1)
• Carboplatin/paclitaxel/dostarlimab-gxly (category 1)
• Carboplatin/paclitaxel/trastuzumab (for HER2-positive uterine serous carcinoma)
• Carboplatin/paclitaxel/trastuzumab (for HER2-positive carcinosarcoma)
Useful in Certain Circumstances
(Biomarker-directed therapy: After prior platinum-based therapy including neoadjuvant and adjuvant)
• MMR-proficient (pMMR) tumors
Lenvatinib/pembrolizumab (category 1)
• TMB-H tumors
Pembrolizumab
• MSI-H/dMMR tumor
Pembrolizumab
Dostarlimab-gxly

p53 do best if they receive adjuvant chemotherapy after initial treatment. Adjuvant radiation appears to benefit the NSMP group. The staging guidelines for endometrial cancer are now including these tests to help guide therapy, particularly in early-stage therapy.

Additionally, other tests are recommended depending on the tumor histology. Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) testing (with the addition of HER2 fluorescence in situ hybridization [FISH] for equivocal (IHC) is recommended for all serous and carcinosarcoma tumors because there are effective HER2 targeting therapies. HER2 testing for p53 abnormal carcinomas regardless of histology can also be considered. NTRK gene fusion testing should be considered for metastatic or recurrent endometrial carcinoma.

A significant amount of research has focused on converting a cold tumor to hot so all tumors would respond to immunotherapy. One approach is to add chemotherapy and immunotherapy together. Two trials of this approach were published in 2023 which changed the standard of care for treating advanced/metastatic endometrial cancer.

The addition of pembrolizumab or dostarlimab to chemotherapy significantly improves progression-free survival (PFS). In the 12-month analysis of the pembrolizumab/carboplatin/paclitaxel study that led to FDA approval for first-line use, Kaplan-Meier estimates of PFS in a dMMR cohort were 74 percent in the pembrolizumab group and 38 percent in the carboplatin/paclitaxel group (hazard ratio for progression or death, 0.30; $p < 0.001$), a 36 percent difference in absolute risk.[13] In the proficient MMR cohort, median PFS was 13.1 months versus 8.7 months (hazard ratio, 0.54; $p < 0.001$) which is not as impressive as the dMMR cohort results but still statistically significant. One issue with this trial is the short follow-up of 12 months but longer-term data will hopefully show sustained benefit. In the dostarlimab trial leading to FDA approval for first-line use, in the MSI-H/dMMR population, estimated PFS at 24 months was 61.4 percent in the dostarlimab/carboplatin/paclitaxel group and 15.7 percent in the carboplatin/paclitaxel group (hazard ratio for progression or death, 0.28; $p < 0.001$).[14] In the overall population including proficient MMR, PFS at 24 months was 36.1 percent versus 18.1 (hazard ratio, 0.64; $p < 0.001$). Overall survival at 24

months was 71.3 percent versus 56.0 percent (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87).

Thus, based on the current data showing improved PFS and OS, multiagent regimens that include immunotherapy are preferred for advanced disease, if tolerated.[8] Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) and carboplatin/paclitaxel/dostarlimab is now NCCN recommended first-line treatment of advanced endometrial cancer (Exhibit 2).[8] This was a substantial change in the guidelines between the January 2023 update when just carboplatin/paclitaxel was recommended and the January 2024 update. Patients with HER-2 positive disease should receive trastuzumab with chemotherapy combination.

The combination of immunotherapy with chemotherapy does increase the risk of adverse events compared to either alone. To maximize outcomes and value of care, attention to anticipating and managing the typical adverse events of taking the brakes off the immune system with immunotherapy and the well-known adverse events of carboplatin/paclitaxel are very important.

Trials are ongoing which may lead to future advances in treating this cancer. In HER2 disease, targeting HER2 two different ways with the addition of pertuzumab to chemotherapy/trastuzumab is being studied. Since HER2 disease typically is microsatellite stable (cold), the addition of immunotherapy to HER2 targeted therapy needs to be investigated. Poly-ADP ribose polymerase (PARP) inhibitors in combination with immunotherapy are also being investigated as maintenance therapy after initial treatment for advanced/metastatic disease and additional studies of pembrolizumab plus lenvatinib compared to chemotherapy are ongoing.

Conclusion

Endometrial cancer incidence is increasing, and disparities exist in survival based on race/ethnicity. Movement toward biomarker-directed therapy in endometrial cancer is improving outcomes for patients. The standard of care for first-line treatment of metastatic/recurrent disease recently changed dramatically. Continued consideration around toxicity management to maximize value-based care is essential.

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Best Practices in the Treatment and Management of Acute Myeloid Leukemia: Managed Care Decision-Making in an Evolving Landscape

Jeffrey E. Lancet, MD

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Summary

Since 2017, numerous therapies have come to market which are improving survival in those with acute myeloid leukemia (AML). There are issues with the use of these highly potent oral cancer medications in the community which managed care can help address.

Key Points

- Multiple new therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults.
- Unique toxicity profiles for many of the new drugs, along with high acuity of AML patients, will require resources and excellent communication for optimal management in the community.
- The inflated cost of oral AML medications is a major challenge to cost containment.

ACUTE MYELOID LEUKEMIA (AML) IS THE most usual form of acute leukemia in adults. Still, AML is rare overall, accounting for only about 1 percent of all cancers. The median age at diagnosis is 69 years and the five-year relative survival is 31.7 percent.[1]

The traditional approach to treating AML was to treat those who were in better physical shape, with intensive chemotherapy for induction followed at remission by additional chemotherapy or allogenic stem cell transplant. Those who could not tolerate this regimen were given supportive care. Intensive curative intent chemotherapy regimens with or without a stem cell transplant remains the most effective option for those who can tolerate such therapy. The major changes in AML treatment have occurred for those who are unable to tolerate intensive therapy.

Several oral therapies have changed the treatment landscape for AML for those who are unable or unwilling to receive chemotherapy-based treatment and for those with specific mutations. Exhibit 1 shows the many new therapies approved since 2017. Two of the newest agents target common mutations are FMS-like tyrosine kinase 3 (FLT3) mutation and isocitrate dehydrogenase 1 (IDH1) mutation. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation. FLT3 ITD mutations occur in 20 to 25 percent of AML cases and result in poor prognosis and high rates of relapse after treatment. FLT3 TKD mutations occur in 5 to 10 percent of cases.[2] Quizartinib is the newest FLT3 inhibitor and is indicated for first-line treatment of FLT3+ AML. This agent and midostaurin, another FLT3 inhibitor, improve survival in first-line treatment of AML.[3,4]

Exhibit 1: New Therapies Approved for AML 2017 – 2023

Year Approved	Drug	Class/Mechanism	Primary Indication
2017	Midostaurin (Rydapt®)	FTL3 inhibitor	FTL3+, new AML
2017	Gemtuzumab Ozogamicin (Mylotarg®)	CD33 antibody-drug conjugate	CD33+, new AML
2017	Daunorubicin-cytarabine liposome (Vyxeos®)	Cytotoxic Chemotherapy	New secondary AML
2017	Enasidenib (Idhifa®)	IDH2 inhibitor	IDH2+ relapse/refractory AML
2018	Venetoclax (Venclexta®)	BCL2 inhibitor	New, elderly, AML (combined with azacitidine, decitabine, or cytarabine)
2018	Gilteritinib (Xospata®)	FLT3 inhibitor	FLT3+ relapse/refractory AML
2018	Glasdegib (Daurismo®)	SMO inhibitor	New, elderly AML (combined with cytarabine)
2019	Ivosidenib (Tibsovo®)	IDH1 inhibitor	IDH1+ AML (new or relapse/refractory)
2020	Oral Azacitidine (Onureg®)	Hypomethylating agent	Maintenance in CR1
2022	Olutasidenib (Rezlidhia®)	IDH1 inhibitor	IDH1+ AML (relapse/refractory)
2023	Quizartinib (Vanflyta®)	FLT3 inhibitor	FTL3+, new AML

Median overall survival with quizartinib for three years after the end of chemotherapy was 31.9 months versus 15.1 months for placebo (hazard ratio 0.78, $p = 0{\cdot}032$).[4] The presence of a FLT3 mutation is an indication for incorporation of FLT3 inhibitors with induction and consolidation chemotherapy in fit patients and followed by the FLT3 inhibitor maintenance.

Approximately 20 percent of patients with AML have an IDH1 or IDH2 mutation.[5] IDH is an enzyme in the citric acid cycle. Mutant IDH1 produces 2-hydroxyglutarate which alters DNA methylation and leads to a block in cellular differentiation.[6] Olutasidenib is the newest IDH1 inhibitor, joining ivosidenib. Olutasidenib is currently FDA approved for relapsed/refractory IDH1+ AML.

One of the most used oral agents in patients who are unfit for chemotherapy is venetoclax. Venetoclax promotes apoptosis by selectively inhibiting B cell lymphoma two (BCL-2). In AML, overexpression of BCL-2 enables cancer cells to evade apoptosis via sequestering proapoptotic proteins. Venetoclax selectively binds to BCL-2, thereby freeing proapoptotic proteins to initiate apoptosis. In combination with azacitidine, a hypomethylating agent used alone in the past, venetoclax significantly improves survival in first-line treatment of AML.[7]

There are several issues with venetoclax use in AML. There is limited efficacy in p53 mutant AML. Efficacy in patients who develop AML but were treated with a hypomethylating agent for an antecedent hematological disorder is unclear. Lastly, venetoclax is a highly myelosuppressive drug administered in an outpatient setting which can lead to many adverse events.

In addition to myelosuppressive issues with venetoclax, the other newer therapies for AML have some unique adverse events of which clinicians encountering patients treated with these agents need to be aware. For example, IDH inhibitors can cause differentiation syndrome (DS) which is a serious potentially fatal adverse event. IDH inhibitors can produce drug-induced differentiation of leukemic cells. Proliferation of differentiated leukemic cells can alter cytokine balance, leading to tissue damage and inflammation. Signs and symptoms of DS include unexplained fever, dyspnea, pleural or pericardial effusions, pulmonary infiltrates, hypoxia, and acute kidney injury. DS occurs in 10 to 15 percent of patients treated with an IDH inhibitor and may occur late in therapy. The median time to DS is 30 days after starting therapy but can be much longer. Treatment is corticosteroids, supportive care, and holding the IDH inhibitor. Other usual

Exhibit 2: Costs of New Medications are High

Drug	Average Wholesale Price
Midostaurin	$170.24 per 25 mg tablet
Gilteritinib	$300.00 per 40 mg tablet
Enasidenib	$1,029.79 per 100 mg tablet
Ivosidenib	$522.30 per 250 mg tablet
Venetoclax	$111.51 per 100 mg tablet
Glasdegib	$338.50 per 25 mg tablet
Oral Azacitidine	$1,650.14 per 200 mg tablet
Olutasidenib	$536.67 per 150 mg tablet
Quizartinib	$546.00 per 17.7 mg and 26.5 mg tablet

adverse events of cancer treatment such as nausea, vomiting, thrombocytopenia, and neutropenia also commonly occur. Patients and clinicians need to understand the potential adverse events of these potent oral cancer treatments and how to manage these in the community.

All new agents approved since 2017 have led to a paradigm shift from a binary choice of intense chemotherapy or supportive care to diverse options including intense chemotherapy with or without targeted agents, oral but potent therapies for those who only received supportive care in the past, and numerous options for relapsed/refractory disease. Much of AML care has shifted from hospitals to the home with the introduction of so many oral agents.

Challenges in this transition to primarily outpatient care are numerous. These include long travel distances from the primary treating center for patients, education of community-based oncologists in management of diseases with less familiarity, need for frequent visits to community oncologists, and resource strains (e.g., blood products). Transportation costs for patient/families, communication with tertiary specialists, and accessibility of medical records between primary treating center and community-based providers are all substantial issues to overcome. There are questions whether these challenges affect overall efficacy of the treatment regimens and negatively impact any potential cost savings.

The cost of care for chemotherapy treated AML patients is largely driven by inpatient costs.[8] Even without chemotherapy, treatment of AML can be costly. One study from 2018 of an older AML patient found an average cost of $25,000 per month for care and this was when monthly medication costs were $450.[9] Assuming an average 10-month life expectancy for AML patients over 60 years of age, who are the primary group for lower intensity therapy, this equates to a cost of $250,000 for AML care over the average life of a patient or an estimated $4.8 billion for all the older AML patients in the United States (U.S.).

The new oral medications are now the primary cost driver of AML care. Exhibit 2 shows the per unit average wholesale cost of the oral therapies but some of these require more than one dose daily. Annual costs can be almost $200,000. A few cost-effectiveness studies of the new therapies have been published. An analysis of gilteritinib use for relapsed/refractory FLT3+ AML found that it led to an increase of 1.29 discounted quality-adjusted life-years (QALYs) at an additional cost of $148,106 versus salvage chemotherapy, corresponding to an incremental cost-effectiveness ratio (ICER) of $115,192 per QALY. For best supportive care, results were an increase of 2.32 discounted QALYs, $249,674, and $107,435, respectively.[10] In another analysis, venetoclax/azacitidine use in older, unfit people for first-line treatment was associated with an improvement of 0.61 QALYs compared with azacitidine alone. However, the combination led to significantly higher lifetime healthcare costs (incremental cost, $159,595), resulting in an ICER of $260,343 per QALY gained.[11] The analysis noted that the price of venetoclax would need to decrease by 60 percent for venetoclax/azacitidine to be cost-effective at a willingness-to-pay threshold of $150,000 per QALY.

In addition to the acquisition costs of the medications, there are other barriers to cost savings in AML with the newer medications. Outpatient therapies are still complex and potent, which could lead to a higher risk of adverse events and hospitalizations amongst patients cared for by less experienced clinicians. AML remains a disease with very limited curative potential, but this is changing. As people live longer with the disease, they will accumulate financial toxicity from their therapies. Extremely high drug prices make it mandatory to manage patients appropriately so any savings are not offset by increased hospitalization rates. Few treatment strategies currently employ discontinuation of oral or maintenance therapies and these therapies are continued until disease progression. There are no published studies of pathway utilization and clinical and financial outcomes in AML—these are needed. In addition, studies are needed on patient financial burden of the newer medications and the impact on therapeutic outcomes.

Conclusion

Multiple new therapies for AML are improving outcomes and shifting care toward the outpatient setting, especially for older adults. Unique toxicity profiles for many of the new drugs, along with high acuity of AML patients, will require resources and excellent communication for optimal management in the community. The inflated cost of outpatient AML prescription drugs (especially as outcomes improve), provides a major challenge to cost containment. Future research should focus on patient financial burden of new oral AML drugs and effects on outcomes.

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Incorporating the Latest Treatment Changes in Prostate Cancer: Applying the Latest Evidence to Improve Outcomes

Daniel P. Petrylak, MD

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Summary

Tremendous advances have been made in the treatment of prostate cancer, especially for resistant disease. The most important advance has been the earlier use of combination therapy with androgen receptor targeting agents or chemotherapy in the setting of hormone sensitive metastatic disease rather than waiting until the disease is no longer hormone sensitive. This improves overall survival.

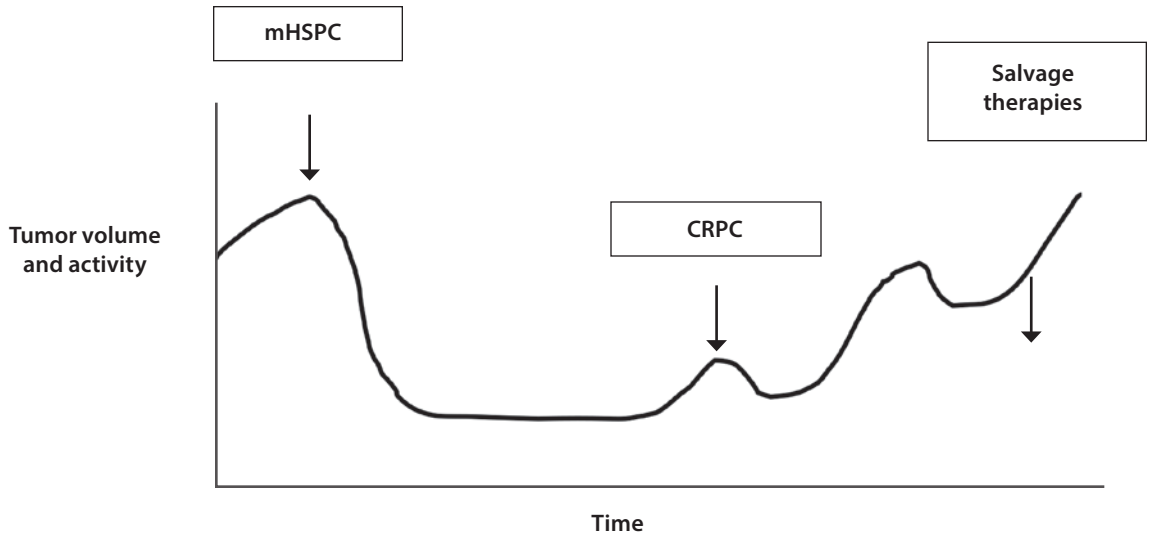
Key Points

- In hormone sensitive metastatic disease, intensification of treatment with either doublet or triplet therapy is standard treatment.
- All prostate cancer patients should be tested for microsatellite instability (MSI), tumor mutational burden, and DNA repair mutations to identify eligibility for selected therapies.
- Once metastatic prostate cancer is no longer hormone sensitive (mCRPC), checkpoint inhibitor immunotherapy is an appropriate treatment for those patients who have MSI-high (MSI-H) and PARP inhibition for those patients with DNA repair mutations.
- Lu177 PSMA is FDA approved for patients with mCRPC who have been treated with prior antiandrogen therapy and are prostate-specific membrane antigen (PSMA) scan positive.

IN CLINICALLY LOCALIZED PROSTATE cancer, surgery and radiation are potentially curative but as many as one-third of patients will have disease progression after the initial treatment. Before recent changes to the standard of care, patients with metastatic disease were offered androgen deprivation therapy (ADT) with gonadotropin hormone-releasing hormone agonists and antagonists to achieve a castration level of testosterone. ADT results in dramatic tumor reduction and improvement in symptoms but after 18 to 24 months the prostate specific antigen (PSA) levels begin to rise and disease increases on bone scans (Exhibit 1). This is now an androgen independent state (metastatic castrate resistant prostate cancer, mCRPC). Treatment options once the disease is at this stage are transiently effective and include abiraterone, enzalutamide, sipuleucel T, pembrolizumab, chemotherapy (docetaxel, cabazitaxel), radium 223, and poly ADP ribose polymerase (PARP inhibitors). mCRPC is a lethal stage of disease with about 33,000 men dying every year in the United States.

Castrate resistance, defined as increasing PSA levels or progressive disease on imaging despite a castrate level of serum testosterone (< 50 ng/dL),

Exhibit 1: Treatment of Metastatic Prostate Cancer



mHSPC = metastatic hormone sensitive prostate cancer;
CRPC = castrate resistant prostate cancer

develops through several mechanisms. Examples are androgen receptor mutations and splice variants and cancer cells learning how to make their own testosterone.[1] More than one-third of cases are the results of androgen receptor deregulation through amplification or overexpression. All of these alterations can lead to restored androgen receptor activity.

The choice of therapy for metastatic prostate cancer is based on clinical characteristics (symptomatic versus asymptomatic, visceral versus non-visceral disease, prior docetaxel use, and other prior treatments), whether the disease is still hormone sensitive or not, and biological markers (microsatellite instability [MSI], tumor mutation burden and DNA repair deficiency mutations). Adverse events of the various agents are also considered.

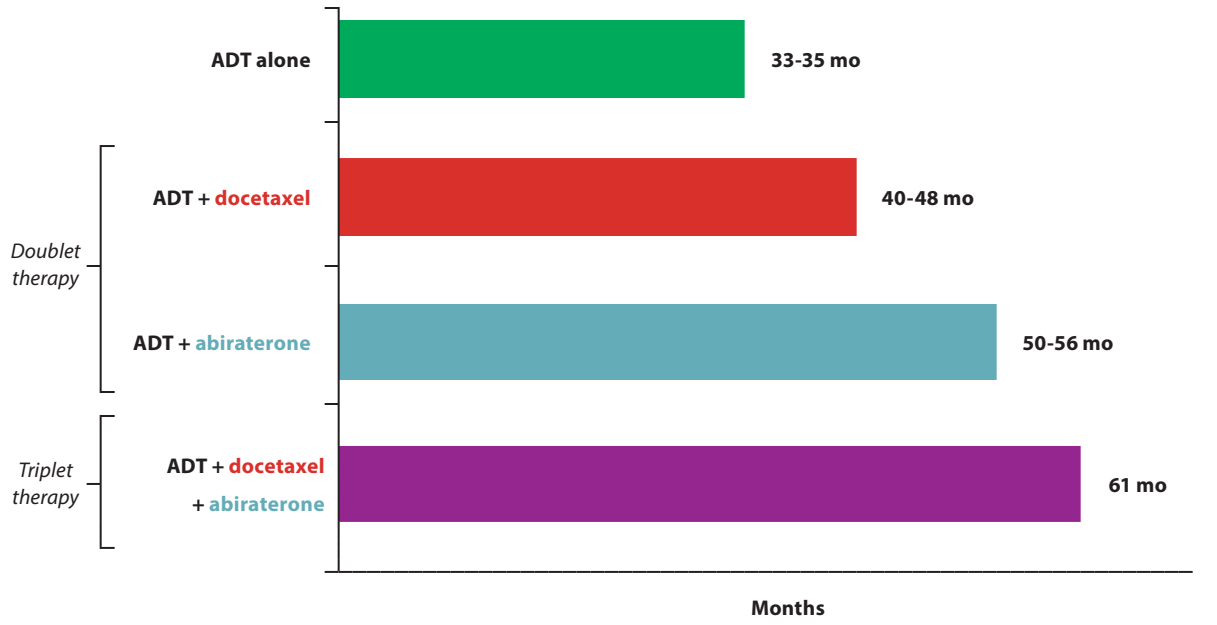
ADT had been the mainstay of managing metastatic hormone sensitive prostate cancer (mHSPC) but intensifying therapy beyond ADT alone has shown improved survival and is the new standard of care. Doublet therapy with the addition of androgen receptor (AR)-directed therapy (abiraterone/prednisone, apalutamide, enzalutamide) to ADT and triplet therapy with chemotherapy (docetaxel) and AR-directed therapy (abiraterone/prednisone, darolutamide) and ADT are National Comprehensive Cancer Network (NCCN) Category 1 recommendations for mHSPC.[2] Doublet therapy decreases risk of death by 34 to 40 percent compared to ADT alone.[3-6] Triplet therapy decreases risk of death by 25 to 32 percent compared to ADT plus docetaxel alone.[7,8] As shown in Exhibit 2, treatment intensification appears to be especially beneficial in those with high-volume disease.[3,4,7,9,10] Radiation therapy to the prostate in addition to ADT in the setting of low-volume disease is also an option.

It is important to note that adverse event rates are greater with doublet and especially triplet therapy. Exhibit 3 highlights some factors in choosing which agents to include in a regimen for mHSPC. Triplet therapy is often used in fit patients with aggressive disease or features suggesting less dependence on the AR (high volume of metastatic disease, low PSA given volume of disease, high grade/poorly differentiated).

Once a patient has mCRPC, there are now numerous treatment options and the choice of therapy will depend again on those factors discussed earlier. Prior treatment plays a key role in the selection of treatment at this stage. Three classes to highlight are immunotherapy with checkpoint inhibitors, PARP inhibitors, and PSMA radiopharmaceuticals.

Pembrolizumab, a checkpoint inhibitor, is FDA approved for treatment of MSI-H cancers so it is an option for mCRPC with MSI-H which is about 2 percent of those with mCRPC. The Keynote 199 trial demonstrated a response in mCRPC with pembrolizumab.[11] About 11 percent of subjects experienced a 50 percent or greater PSA reduction from baseline and about 50 percent of subjects

Exhibit 2: Median OS with Treatment Intensification in De Novo High-Volume mHSPC[3,4,7,9,10]



*Cross-trial comparisons have significant limitations.
OS = overall survival; mHSPC = metastatic hormone sensitive prostate cancer; ADT = androgen deprivation therapy

had some tumor reduction. Whether this therapy impacts overall survival (OS) in mCRPC is not yet known. Because there is an approved therapy, all patients with mCRPC should have an MSI analysis to see if they qualify.

A newer option for selected patients with mCRPC is PARP inhibitors. PARP repairs double-stranded breaks in DNA. Cells with breast cancer (BRCA) mutations only have PARP as an option to repair double-stranded breaks and thus PARP inhibition leads to cell death. About 12 percent of men with prostate cancer have BRCA 1 and 2 mutations which would make their cancers susceptible to PARP inhibition.[12] Other homologous recombination repair (HRR) mutations also increase susceptibility to PARP inhibition. In men with mCRPC who had disease progression while receiving enzalutamide or abiraterone and who had alterations in HRR genes including BRCA 1 and 2, olaparib was associated with longer progression-free survival (3.8 months) and better measures of response and patient-reported end points than either enzalutamide or abiraterone.[13] Interim median OS with olaparib was 17.5 months compared to 14.3 months with AR-targeted therapy but final OS results have not yet been published. In a similar study with rucaparib, the duration of radiologic progression-free survival (rPFS) was significantly longer with rucaparib than with a control medication among patients who had mCRPC with a BRCA alteration (4.8-month difference).[14] OS data have not yet been reported. Importantly, the olaparib and rucaparib trials found that PARP inhibition was not as effective in those with ATM mutation (one of the known HRR mutations) compared to BRCA 1 and 2.

Olaparib, niraparib, and talazoparib have also been studied in combination with various AR targeting agents. The combination of PARP inhibitor and AR targeting agents has synergy. It enhances blockade of AR signaling through various mechanisms and induces "BRCAness" through decreased HRR gene expression, decreased double-strand break repair, and radiosensitivity.[15] The combinations improve rPFS and in one trial improved OS, however, final survival data are not yet available from the talazoparib trial but in the olaparib trial it was not statistically different.[15-18] A meta-analysis of the combination trials with talazoparib and niraparib found a 16 percent reduction in the risk of death among patients who received the combination.[19] Talazoparib/enzalutamide, olaparib/abiraterone, and niraparib/abiraterone are included in the NCCN Guidelines as Category 1 recommendations for first-line therapy in those who have not had prior docetaxel or novel

Exhibit 3: Treatment Selection for mHSPC

Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Docetaxel
• Generic. • Has to be given with prednisone. • Requires K+/LFT/BP monitoring. • Concern for long-term hypertension and prednisone adverse events. • Less fatigue than others. • Can intensify to triplet therapy.	• Less monitoring. • Concern for neurocognitive issues.	• Less monitoring. • Concern for rash and neurocognitive issues.	• Less monitoring. • Can intensify to triplet therapy.	• Least expensive. • Completed after 6 cycles. • Offer while chemo fit. • Potential for new/worsened neuropathy. • Can consider stopping early if exceptional responder/not tolerating chemo.

hormonal therapy and have HRR mutations.[2]

A new imaging technique for prostate cancer-prostate-specific membrane antigen-positron emission tomography (PSMA-PET) is being used to identify patients eligible for a new radiopharmaceutical therapy. PSMA is a well-established, prostate tissue-restricted, cell membrane target that can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in over 80 percent of men with metastatic disease.[20] Because of the increased sensitivity and specificity of PSMA-PET for detecting micro-metastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the NCCN Guidelines do not recommend that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT can serve as an equally effective, if not a more effective front-line imaging tool for patients.[2] PSMA PET/CT should be done in patients at initial diagnosis if there is a high suspicion for metastatic disease, i.e., NCCN unfavorable intermediate risk, high risk, or very high risk; high Decipher, Prolaris, or Oncotype GPS scores or risk of metastasis over 5 percent by nomogram. PSMA PET/CT should be done in all patients at initial biochemical recurrence and considered for patients with subsequent recurrence and/or progression. PSMA imaging is going to find many more metastatic cases than conventional imaging but whether earlier therapeutic intervention is beneficial is not yet known.

Lutetium Lu 177 vipivotide tetraxetan, a radiopharmaceutical, is the newest therapy for mCRPC. The radionuclide lutetium-177 is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to the cells, as well as to surrounding cells, and induces DNA damage which leads to cell death. This agent plus standard care compared to standard care significantly prolonged both rPFS (median, 8.7 versus 3.4 months; $p < 0.001$) and OS (15.3 versus 11.3 months; $p < 0.001$).[21] The NCCN Guidelines list this therapy as a Category 1 treatment option for PSMA-positive mCRPC with prior docetaxel and AR-targeted treatment.[2] This and other PSMA radiopharmaceuticals are being evaluated in earlier prostate cancer disease states.

Conclusion

In mHSPC, intensification of treatment with either doublet or triplet therapy is standard treatment. All prostate cancer patients should be tested for MSI, mutational burden, and DDR mutations to identify eligibility for selected therapies. In mCRPC, checkpoint inhibitor immunotherapy is an appropriate treatment for those patients who have MSI and PARP inhibition for those patients with DNA repair mutations. Lu 177 PSMA is FDA approved for patients with CRPC who have been treated with prior antiandrogen therapy and are PSMA positive.

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Advanced Insights for Patients with Psoriasis: Understanding the Latest Clinical Evidence and Shared Decision-Making Options

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Summary

Although biologics receive a great deal of attention when the treatment of psoriasis is discussed, topical treatments still have a place in therapy, particularly for those with more limited disease. Two new medications reached the market in 2022 and appear to have some benefits over older topicals.

Key Points

- Nonadherence with topical medications is an issue.
- Patients want topical treatments that are non-ointment based due to greasiness, have quick results, and are easy to use on a regular basis.
- A cream formulation of calcipotriene and betamethasone improves patient acceptance over other formulations.
- Tapinarof and roflumilast creams offer patient-acceptable cream formulations and long-term use without major adverse events.
- Cost and insurance coverage may limit the use of agents which are likely to improve patient adherence.

PSORIASIS IS A COMMON CHRONIC MULTISYSTEM inflammatory skin disease with a variety of clinical manifestations and comorbidities that extend beyond psoriatic arthritis (PsA). It affects more adults than children with the peak age of diagnosis in those 20 to 30 and 50 to 60 years of age. Prevalence increases with distance away from the equator. Worldwide between 0.5 to 11.4 percent of adults and up to 1.4 percent children are affected.[1] Prevalence in the United States (U.S.) is about 3.0 percent.[2]

Understanding the approach to treating psoriasis is important for several reasons. Psoriasis is common, affecting over 125 million individuals worldwide, but it is often undiagnosed, undertreated, or untreated. Psoriasis treatment has evolved beyond topical corticosteroid monotherapy and now there is no shortage of effective treatment options. Lastly, psoriasis is more than skin deep, and dermatologists are the quarterbacks of the psoriasis treatment team.

There are cycles of sustained inflammation and remission with psoriasis caused by dysregulation in both innate and adaptive immunity in those with predisposing genetic factors.[3]

Dysregulation leads to uncontrolled keratinocyte proliferation and impaired keratinocyte differentiation. Psoriasis presents with a spectrum of features that usually involve erythema, thickening, and scaling.[3,4] The main types are chronic plaque, guttate, erythrodermic, pustular, and inverse. Psoriasis also affects the scalp, nails, hands, and feet.

Exhibit 1: Recommendations for Treatment[6-8]

Topicals
• Class 1 to 5 TCS for up to 4 weeks for non-intertriginous plaque psoriasis.
• Class 1 to 7 TCS for a minimum of up to 4 weeks is recommended as initial and maintenance treatment of scalp psoriasis.
• The use of topical corticosteroids for up to 12 weeks can be considered if done under the careful supervision of a physician.
• Long-term use of vitamin D analogs for mild-to-moderate psoriasis.
• Combined TCS-vitamin D analogs for scalp and body for long-term use.
• Combined Class 2 to 5 TCS-tazarotene for mild-to-moderate psoriasis and to decrease treatment duration and increase remission.
Oral Agents
• Methotrexate for moderate-to-severe psoriasis but less effective than TNF inhibitor biologics.
• Apremilast for moderate-to-severe psoriasis.
• Cyclosporin for severe psoriasis, recalcitrant disease, erythrodermic, or pustular.
Biologics
• High strength of recommendation and level of evidence across all biologic classes.
• Preponderance of data for TNF inhibitors but others have largely caught up.
• IL-23 and IL-17 agents are more efficacious in general but have limited head-to-head studies.
• Good data for combination therapy with TCS, less for other adjunctive treatments.
• TNF inhibitors and IL-17 agents initially with more joint data but IL-23s catching up.
• Long-term data still accumulating but have looked very promising

TCS = topical corticosteroid
Corticosteroids are classified based on potency with Class 1 being ultrapotent, 2 and 3 high, 4 and 5 moderate, and 6 and 7 low.

Chronic plaque psoriasis is the most common variant of psoriasis with sharply demarcated, symmetrically distributed, scaly papules and plaques. Common areas include the scalp, extensors, umbilicus, pre-sacrum, as well as the hands and feet. Lesions may be focal or widespread. Body surface area (BSA) that is affected does not reflect severity on its own. For example, the hands and feet can be affected which is a small surface area but this can be debilitating if the person cannot use their hands or walk.

When considering treatment, it is important to know that the burden of psoriasis goes beyond skin lesions. Comorbidities and other symptoms need to be addressed.[5] Because this is a systemic inflammatory disease, there are various comorbidities including psoriatic arthritis, cardiovascular disease, metabolic syndrome, inflammatory bowel disease, renal disease, uveitis, and hepatic disease. Symptoms including itch and sleep disturbance can significantly affect quality of life. Quality of life (QOL) considerations include mental, physical, and social burdens of the disease.

Psoriatic arthritis (PsA) is an inflammatory oligoarthritis of peripheral joints (small joints of the hands and feet, knees, wrists, and elbows) with similarities to rheumatoid arthritis. Some patients may also have inflammatory arthritis of the spine. It is important to screen for PsA as skin disease usually precedes joint disease by years and uncontrolled arthritis may result in irreversible joint damage. Prevalence of PsA among psoriasis patients is approximately 30 percent with an onset time of 10 to 11 years after the start of psoriasis symptoms.[5]

Mild-to-moderate psoriasis can be managed with topical therapy. Moderate-to-severe disease requires oral, biologic, and/or phototherapy with or without topicals. Measures of severity used to determine which therapy would be indicated and to measure treatment efficacy include psoriasis area and severity index (PASI) which grades erythema, induration, and desquamation in four body areas, BSA, physician

Exhibit 2: The Words That Patients and Healthcare Providers Use Highlight the Major Problems with Topicals

Commonly Said by Patients	Commonly Said by Healthcare Providers
• "The topical stopped working"	• "This case is refractory to topical therapy"
• "The topical never worked"	• "My [xyz] patients never seem to respond well to topicals"
• "I've already tried so many topicals and none of them have worked"	• "My colleagues and I get different results"
• "Every time I try a new topical it only works for a little while"	• "This topical is hit and miss"
• "It comes right back when I stop using it"	• "This does not match the clinical trial data"

global assessment (PGA), PGA x BSA, psoriasis symptom inventory (PSI), itch severity scores, and dermatology life quality index (DLQI).

Conventional topical therapy includes use of topical corticosteroids (TCS), topical calcineurin inhibitors (tacrolimus, pimecrolimus), vitamin D analogs (calcipotriene, calcitriol), tazarotene (retinoid), salicylic acid, anthralin (dithranol – a polycyclic aromatic hydrocarbon derivative), coal tar/liquor carbonis distillate, and combination therapies. Emollients are important in all patients with psoriasis to moisturize the skin and help restore barrier function. Exhibit 1 presents the topical treatment recommendations which have the highest level of evidence from the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF).[6-8]

Conventional oral, non-biologic therapies which are FDA approved for psoriasis include methotrexate, apremilast (oral phosphodiesterase-4 [PDE4] inhibitor), cyclosporine, and acitretin (oral retinoid). Other agents have also been used but are not FDA approved. Exhibit 1 shows the recommendations for oral therapy with the highest level of evidence.[6-8] Use of methotrexate cyclosporin, and acitretin are limited because of the potential for adverse events and need for laboratory monitoring compared to biologics.

Biologics approved for treating moderate-to-severe psoriasis include tumor necrosis factor (TNF) inhibitors, anti-interleukin 17 (IL-17), anti-IL-23 and anti-IL-12/23. Exhibit 1 shows the most recent AAD/NPF recommendations.[6-8] The biologics have the best efficacy for moderate-to-severe disease.

A few changes in managing psoriasis have occurred in the last few years. Apremilast now has FDA approval for mild disease in addition to moderate-to-severe. It is the first systemic therapy to be approved for any severity of psoriasis. Spesolimab is the first FDA-approved agent for generalized pustular psoriasis flares. It is an IL-36 receptor antagonist monoclonal antibody given as one or two intravenous doses. Deucravacitinib is an oral tyrosine kinase 2 (TYK2) allosteric inhibitor that was approved for moderate-to-severe psoriasis in 2022. It is the first TYK2 agent and first new oral therapy since 2014. Bimekizumab, the first IL-17 agent that blocks both A and F isoforms was FDA approved in October 2023 for moderate-to-severe psoriasis. Lastly, two new topical agents were FDA approved in 2022 – tapinarof and roflumilast. These two agents are helping the topical landscape change to better align with patient therapeutic goals. None of these new agents nor mild disease indication for apremilast are yet included in the treatment guidelines.

In a 2018 NPF survey, only 20 percent of patients were on systemic medications yet the majority of the patients surveyed had moderate-to-severe disease.[9] Many patients were not satisfied with their treatment noting that it was either not effective enough, were worried about adverse events and long-term safety, frequency of dosing was issue, and treatment was not easy to use. The majority of patients (54.3%) would have preferred to be on an effective topical if one was available.

Unlike in the NPF survey, most patients with psoriasis have mild-to-moderate disease for which topical therapy is recommended. Although topical corticosteroids have been the mainstay of psoriasis treatment for many years, there are issues. The positives with this class are mechanistically targets inflammatory pathogenesis of psoriasis, fast onset (within days), multiple options for potency and vehicle, practical application directly to areas of involvement, patient preference for route of delivery, high strength of recommendation and level of evidence for treatment periods up to four weeks in guidelines, and they are relatively inexpensive and accessible. The downsides are a lack of high quality randomized controlled trials (especially for older agents), mechanistically cannot address all

aspects of psoriasis (negative impacts on epidermal differentiation and systemic inflammation), loss of efficacy over time ("tachyphylaxis"), inconvenient/constant use required, application issues, adverse events, reduced integrity of stratum corneum, reduced ability to recover from injury, cutaneous atrophy/striae, loss of subcutaneous fat, dyspigmentation, systemic absorption with HPA axis suppression, poor strength of recommendation and level of evidence for long-term treatment. The words that patients and healthcare providers use highlight the major problems with topicals, including conventional agents beyond corticosteroids (Exhibit 2).

Adherence to topical use is a key part of the equation that is often overlooked. Intentional non-adherence has been estimated at approximately 40 percent.[10,11] Those who are non-adherent believe that psoriasis and its treatments interfere with QOL and have a perception of increased severity.[10] Nonadherence is a common reason for topical failure. In one Danish study, 44 percent of eligible patients with psoriasis did not fill their new topical prescription within four weeks.[12] Topical medications present a particularly unique burden. They are cumbersome to use if a large BSA or hard to reach place is affected. In one study of individuals without psoriasis who were instructed to apply a fluorescent cream to the entire body, found up to 31 percent of the body was neglected.[13] With topicals, unpleasantness (i.e., messy, greasy, never feeling clean) is one of the worst aspects of treatment.[14] It can also be time consuming to apply topical treatments and one study found it took over 40 minutes daily.[15] Obviously, better topical medication adherence is associated with better treatment outcomes.[15]

To be better adherent, patients want new topical treatments that are non-ointment based due to greasiness, have quick results (1 to 2 weeks of treatment), and are easy to use on a regular basis to prevent discomfort.[16] A combination product of calcipotriene, a vitamin D analogue, and betamethasone dipropionate has become a mainstay of topical psoriasis treatment and is recommended by the guidelines because it negates some of the disadvantages of corticosteroids alone and has synergistic properties. Clinical benefits of the combination are increased efficacy over either alone, rapid onset of action, steroid-sparing effect, favorable safety profile, and reduced risk of skin atrophy and skin thickness, rebound phenomenon, telangiectasia, and tachyphylaxis.[17] However, some formulations of this combination (ointment, foam, suspension) still have a greasiness due to the chemical properties of the two ingredients. A recent cream formulation approved in 2020 uses a newer technology of oil-in-water dispersions with droplets that have robustness from coalescence and are stable without a large excess of surfactant. The cream formulation has been shown to be more effective than the topical suspension formulation in clearing skin and reducing itch.[18] Patient preference for the cream formulation over suspension is primarily driven by reduced greasiness.[19] Unfortunately, access to the branded cream formulation may be limited by insurers because of the substantial cost difference between brand cream and generic ointment and suspension formulations.

Two newer topicals may also fulfill many of the patients' wants because both are once daily creams. Tapinarof, an aryl hydrocarbon receptor (AhR) agonist, is available in a 1 percent cream. AhR senses environmental cues and functions as a master homeostatic regulator of barrier and immune function in the skin.[20] AhR activation results in upregulation of filaggrin, loricrin, and involucrin, Th17 cell differentiation, IL-17, and IL-22 production, Th2 cell differentiation, and IL-4 and IL-5 production. The approval trials for tapinarof included a full spectrum of patient representation across mild, moderate, and severe disease. Tapinarof 1 percent cream once daily was superior to vehicle control in reducing the severity of plaque psoriasis over a period of 12 weeks but was associated with local adverse events (contact dermatitis, folliculitis, itching) and headache.[21] A one-year open label extension including participants from the original trials found that efficacy improved beyond the 12-week trials, with a 40.9 percent complete disease clearance rate.[22] It also found that patients who achieved clear skin could stop the therapy for approximately four months before disease recurred and there was consistent durability on therapy and safety with up to one year of use.

Roflumilast is a PDE4 inhibitor similar to apremilast but is available as a topical 0.3 percent cream instead of oral. PDE4 is the predominant cAMP-degrading enzyme in inflammatory cells and has increased activity in psoriasis and atopic dermatitis. Roflumilast is a highly potent PDE4 inhibitor with an approximately 25- to 300-fold or higher potency than other approved PDE-4 inhibitors (which includes crisaborole for atopic dermatitis and apremilast).[23,24] Roflumilast is approved for psoriasis and currently under investigation for atopic dermatitis and seborrheic dermatitis in cream and foam vehicles. Roflumilast cream is an emollient, water-based (~50% water) cream which contains an emulsifier designed to maintain epidermal intercellular lipids and mirror stratum corneum pH. Among patients with chronic

Exhibit 3: When Should These Newer Therapies be Used?

Calcipotriene/betamethasone	Tapinarof 1% cream	Roflumilast 0.3% cream
• First-line steroidal option (with a better profile than TCS alone) for all severities. • Good for rapid relief and reducing itch burden • Consider patient vehicle preference – may choose cream	• Theoretical first-line non-steroidal option for all severities and body areas. • Patient vehicle preferences (especially for those who've used multiple TCS formulations)	• Theoretical first-line non-steroidal option for all severities and body areas. • Especially good for intertriginous areas • Patient vehicle preference

plaque psoriasis, treatment with roflumilast cream, 0.3 percent, compared with vehicle cream resulted in better clinical status at eight weeks, 34.2 percent higher rate of 75 percent improvement in PASI, and improved itch scores.[25] All levels of disease severity were included in this trial. There were low rates of application site and treatment-related adverse events and discontinuations due to adverse events comparable to vehicle. In the long-term open label follow-up trial, efficacy was sustained out to 64 weeks without any newly identified adverse events.[26]

Overall, tapinarof and roflumilast provide improvements over prior agents. They are relatively fast acting, have predictable long-term results, can be used on multiple body areas, have reasonably low rates of adverse events, long-term safety, good tolerability, and practical once daily application with good patient acceptance. The issue is cost and access.

Exhibit 3 includes the author's professional opinion on when to use the newer agents. Tapinarof and roflumilast are considered theoretical first-line therapies because they have not yet been included in the AAD/NPF guidelines. Calcipotriene/betamethasone, should not be used in the case of preexisting adverse events from long-term TCS use, high BSA affected, or for sensitive or intertriginous body areas. Although tapinarof efficacy improves over time and there are sustained results off therapy, it is slower acting than TCS. There is also a need for more predictive data on topical adverse events and headaches even though the rates are low.

Roflumilast also has efficacy that gets better over time and is especially good for intertriginous areas. It also produced a higher week eight placebo-corrected efficacy compared to tapinarof but these data are from individual clinical trials and not a head-to-head trial. As with tapinarof, roflumilast is slower acting than TCS and more data on adverse events are needed. The biggest limitation with use of these three products is lack of non-commercial insurance for many patients.

Conclusion

Even in the age of biologics, topical therapies still matter, but variable adherence has taught us lessons about what patients are seeking. High potency corticosteroids are still fast and efficacious and a better proprietary cream formulation allows for more targeted use. Non-steroidal topicals offer more flexibility for chronic ongoing therapy with potency that seems to be better than older options – time will tell. However, for now use of these agents comes down to cost and access, which may squeeze the patient out.

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A New Horizon for Patients with Pulmonary Hypertension: Targeting Treatment for Improved Outcomes

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Summary

Pulmonary hypertension (PAH) remains a deadly disease despite therapy advances. Additional treatments on the horizon will introduce a new and exciting era of management with agents targeting the actual pathophysiology of the disease.

Key Points

- PAH remains challenging to diagnose and requires comprehensive assessment, including right heart catheterization.
- Risk assessment is critical for determining prognosis, making treatment decisions, and monitoring over time.
- The current treatment goal is to achieve low-risk status
- The standard of care for most patients is upfront combination therapy with potential escalation to triple therapy.
- Those with high-risk disease should get upfront triple therapy.
- Anti-proliferative therapies will heavily shape the future of PAH therapies.

PULMONARY ARTERIAL HYPERTENSION (PAH), which is a Group 1 pulmonary hypertension, is a complex and devastating disease that causes progressive vasoconstriction and vascular remodeling of the distal pulmonary arteries. PAH includes several subgroups, all having similar pulmonary vascular pathology, clinical characteristics, and management strategies. PAH subtypes are idiopathic, heritable, drug and toxin induced, and PAH associated with HIV, connective tissue disease, portal hypertension, schistosomiasis, or congenital heart disease. Ultimately, most patients with PAH develop right heart dysfunction leading to death.

PAH remains challenging to diagnose and requires comprehensive assessment, including right heart catheterization. Prompt and accurate diagnosis is key to instituting timely and appropriate therapy to improve symptoms and prognosis. The international diagnosis and management guidelines were updated in 2019 and 2022, with a lowering of the hemodynamic threshold for diagnosis to a mean pulmonary artery pressure (PAP) > 20 mmHg and pulmonary vascular resistance (PVR) to greater than or equal to two Wood units (Exhibit 1).[1,2] New diagnostic algorithms and revised indications for screening in at-risk groups have been developed to facilitate early referral to specialist PH centers. Exhibits 2 and 3 show the diagnostic algorithms.[3] This includes fast-track specialist referral pathways for patients who are either clinically high-risk or are at-risk for PAH or chronic thromboembolic pulmonary hypertension (CTEPH).

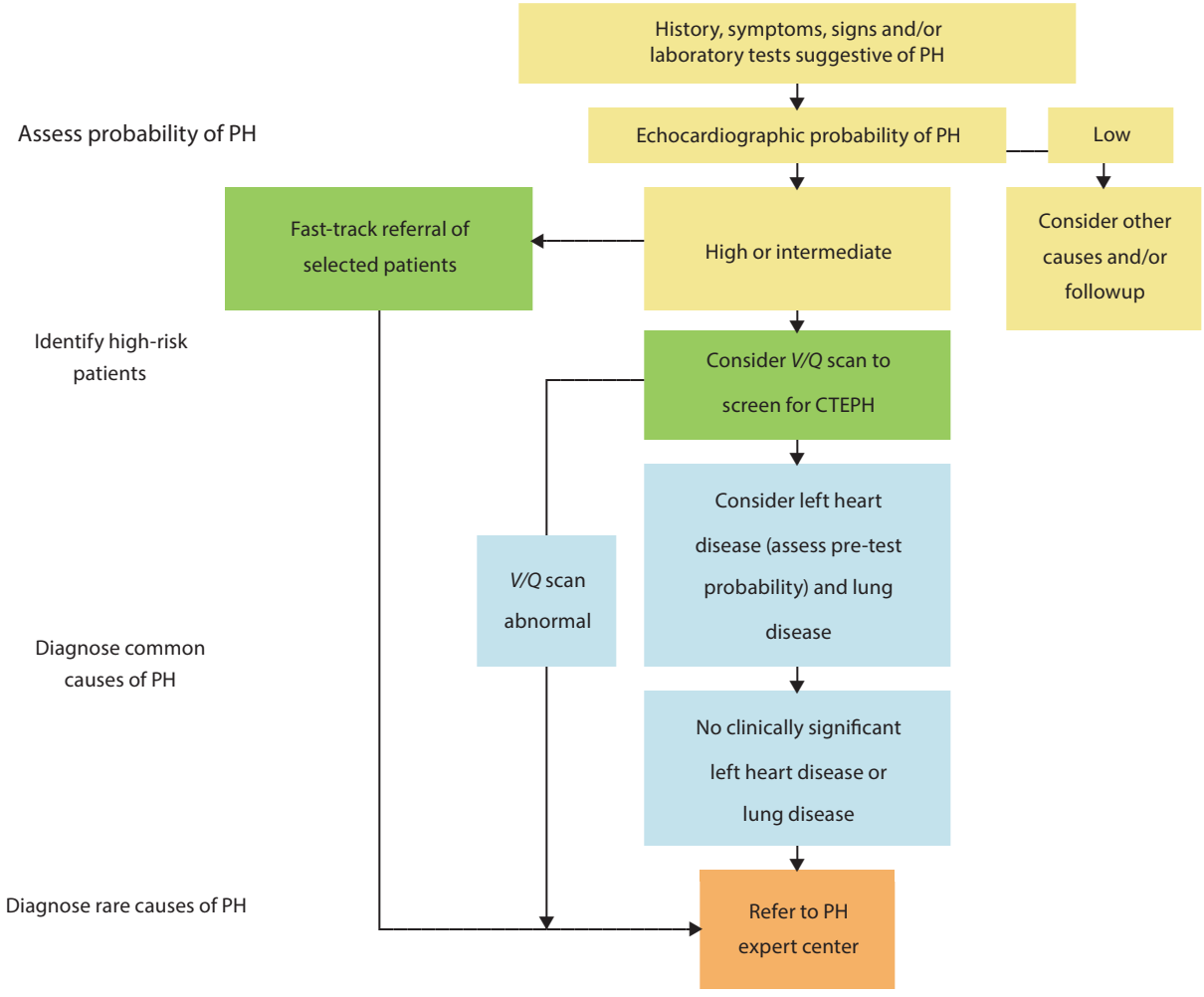
Early referral to a specialist PH center is important because many times patients are misdiagnosed and started on inappropriate, costly, and even harmful medications. One study found that one-third of

Exhibit 1: Updated Definition of Pulmonary Hypertension (PH)[1,2]

		3rd-5th WSPH	6th WSPH	2022 ESC-ERS
PPH	Mean PAP	≥ 25 mmHg	**> 20 mmHg**	**> 20 mmHg**
Pre-capillary PH	PAWP or LVEDP	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg
	PVR	≥ 3 WU	≥ 3 WU	**≥ 2 WU**

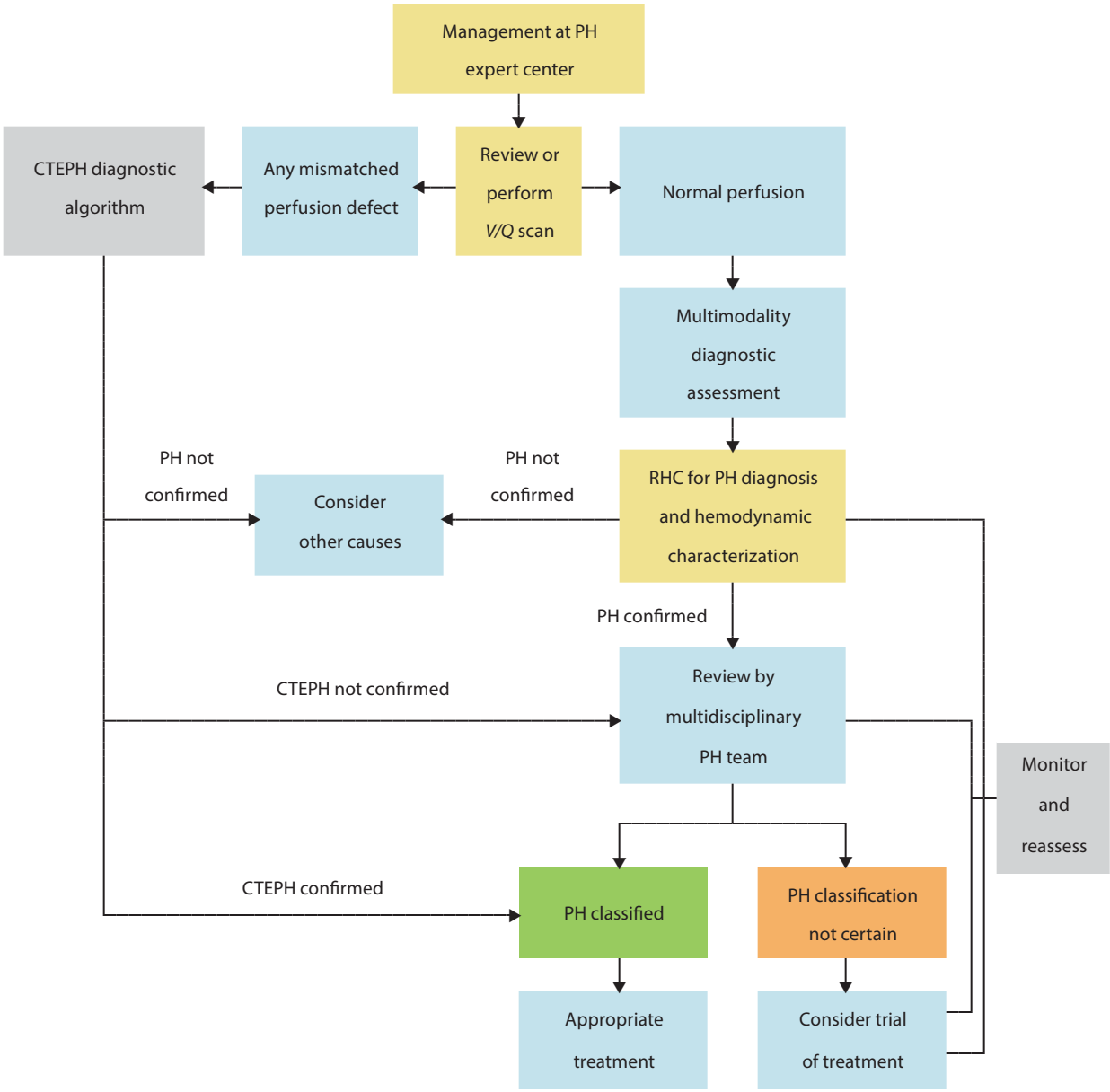
WSPH = World Symposium On Pulmonary Hypertension; ESC-ERS = European Society of Cardiology/European Respiratory Society; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; LVEDP = left ventricular end diastolic wedge pressure; PVR = pulmonary vascular resistance; WU = Woods unit

Exhibit 2: Non-PH Expert Diagnostic Algorithm[3]



CTEPH = chronic thromboembolic pulmonary hypertension ; V/Q = ventilation/perfusion

Exhibit 3: PH Expert Center Diagnostic Algorithm[3]



patients referred to a PH center were misdiagnosed prior to referral.[4] Additionally, 39 percent of patients initiated on PAH-specific medication prior to referral did not have Group I PAH.[4]

The Pulmonary Hypertension Care Centers (PHCC) network in the United States (U.S.) has 85 accredited sites across the county. In addition to being better at diagnosing various types of PH, these centers improve mortality and hospitalization rates. One study found a 32 percent decrease in mortality and 46 percent decrease in hospitalizations.[5] These centers also provide coordinated care with numerous community practitioners.

Despite advances in treatment, PAH is still a fatal disease. From a U.S. registry using modern treatment era data (2015 to 2020 enrollment), the one-, two-, and three-year mortality was 8 percent, 16 percent and 21 percent, respectively.[6] When stratified into low, intermediate, and high-risk PAH, the mortality at one, two, and three years was 1 percent, 4 to 6 percent, and 7 to 11 percent for low-risk; 7 to 8 percent, 11 to 16 percent, and 18 to 20 percent for intermediate risk, and 12 to 19 percent, 22 to 38 percent, and 28 to 55 percent for high-risk,

Exhibit 4: PAH Treatments

Oral Therapy				Inhaled Therapy	Continuous Parenteral Therapy
ERA	PDE-5 Inhibitors	sGC Stimulator	Prostacyclin	Prostacyclins	
Ambrisentan	Sildenafil	Riociguat	Treprostinil	Iloprost	Epoprostenol
Bosentan	Tadalafil		Selexipag	Treprostinil	RTS- Epoprostenol
Macitentan					Treprostinil (SC or IV)

ERA = Endothelin receptor antagonist; PDE-5 = phosphodiesterase; sGC = Soluble guanylate cyclase; RTS = room temperature stable; SC = subcutaneous; IV = intravenous

respectively. Historical survival was 2.5 years from diagnosis so therapy has improved survival with 79 percent of patients still alive at three years.

Treatment for PAH currently targets three pathways that are disrupted in PAH – endothelin, nitric oxide, and prostacyclin. Exhibit 4 shows the available medications by pathway and administration route. Therapy is chosen based on risk for death using risk assessment tools. There are numerous validated tools available that rely on measurements such as the six-minute walk distance (6MWD), functional class, natriuretic peptide levels, and hemodynamics. Some produce three categories of risk – low-, intermediate-, or high-risk whereas others include four categories with low-, intermediate-low, intermediate-high, and high-risk. Four categories are better for tracking changes in risk over time with treatment.[7] The goal of therapy is to achieve low-risk status to minimize mortality.

The current guidelines recommend (based on 3 category risk assessment) initial dual therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase five inhibitor (PDE-5) for those at low- or intermediate-risk and triple therapy (ERA/PDE-5 plus subcutaneous or intravenous prostacyclin) for those with high-risk disease. These regimens have been shown to be better than monotherapy for low- or intermediate-risk and dual therapy for high-risk. One trial found that triple oral therapy with macitentan/tadalafil/selexipag appeared to produce slower disease progression than macitentan/tadalafil with equal benefit on PVR and 6MWD.[8] Based on this trial, most low- and intermediate-risk patients will be fine on two medications but may need additional medications based on risk assessment after the medications are started. In a French registry trial, the survival rate was higher with the use of triple therapy (91% at 5 years) as compared with dual therapy or monotherapy (both 61% at 5 years) ($p < 0.001$).[9] Propensity score matching of age, sex, and pulmonary vascular resistance also showed significant differences between triple therapy and dual therapy (10-year survival, 85% versus 65%). In high-risk patients (n = 243), the survival rate was higher with triple therapy than with monotherapy or dual therapy, whereas there was no difference between monotherapy and double therapy. In intermediate-risk patients (n = 1,134), survival improved with an increasing number of therapies.

After starting initial therapy, the guidelines recommend that risk be assessed. The current guidelines suggest using the four category tools for this assessment.[2] Treatment is intensified if the patient has not achieved low-risk status. For intermediate-low-risk, adding selexipag, a prostacyclin receptor agonist, or switching the PDE-5 inhibitor to riociguat, a soluble guanylate cyclase stimulator, is suggested. For intermediate-high and high-risk patients, adding intravenous or SC prostacyclin inhibitor and evaluating for a lung transplant are both options.

Treprostinil oral and selexipag are more convenient, less risky, and more accessible than the intravenous, inhaled, and subcutaneous prostacyclin analogues. They are attractive for patients not reaching low-risk status with first-line treatment and lower risk of disease progression and hospitalization. Expertise is required for titrating dose and managing adverse events. One-third of patients stop these agents due to adverse events or disease progression within a one year.[10] Importantly, real-world data has shown that oral treprostinil dosing has been inadequate but improved between 2017 and 2020, however,

Exhibit 5: Additional Antiproliferative Investigational Agents for PAH

Compound	Mechanism of Action
Seralutinib (inhaled)	PDGF receptor inhibitor + more
Imatinib (inhaled)	PDGF receptor inhibitor
Rodatristat	Tryptophan hydroxylase inhibitor
KER-012	Activin Receptor IIB fusion protein

PDGF = platelet derived growth factor

dosing may still be inadequate for desired long-term treatment response.[11] All of the prostacyclins have to be dosed appropriately to achieve maximum effect. The target dose of oral treprostinil is 3.5 mg three times daily.

An exciting future therapy—sotatercept—is an activin signaling inhibitor which acts as a ligand trap for members of the transforming growth factor β (TGF-β) superfamily, thus restoring balance between the growth-promoting activin growth differentiation factor pathway and the growth-inhibiting bone morphogenetic protein (BMP) pathway.[12] Imbalance between these two pathways is thought to be the pathogenic mechanism of PAH. Sotatercept is an antiproliferative agent targeting the underlying pathophysiology of the disease. In September 2023, the FDA accepted a new Biologics License Application (BLA) for this agent for priority review for PAH treatment.[13] In a Phase III trial, adults with PAH (WHO functional Class II or III) who were receiving stable background therapy randomly received subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every three weeks.[14] The patients in this trial had long standing PAH (~10 years). The primary end point was the change from baseline at week 24 in the 6MWD. Nine secondary end points were multicomponent improvement, change in PVR, change in N-terminal pro-B-type natriuretic peptide level, improvement in functional class, time to death or clinical worsening, French risk score, and changes in the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) physical impacts, cardiopulmonary symptoms, and cognitive/emotional impacts domain scores. All were assessed at week 24 except time to death or clinical worsening, which was assessed when the last patient completed the week 24 visit. Sotatercept resulted in a greater improvement in exercise capacity (as assessed by the 6MWD) than placebo (median change from baseline at week 24, 34.4 meters versus 1.0 meter). The first eight secondary end points were significantly improved with sotatercept as compared with placebo, whereas the PAH-SYMPACT cognitive/emotional impacts domain score was not. Adverse events with sotatercept included epistaxis, dizziness, telangiectasia, increased hemoglobin levels, thrombocytopenia, and increased blood pressure. The results of this trial are exciting because no previous trial in a population with long-standing disease has shown these same significant benefits. Once sotatercept is approved it will be an add-on therapy for those who have not achieved low-risk status with standard of care treatment. It may also become an option for initial therapy for high-risk patients instead of parenteral prostacyclin. Eventually, it may be a therapy that all PAH patients receive upfront. This therapy works on the pathogenesis of the disease unlike the already approved therapies that work downstream to minimize the impact of PAH-related changes in the lung vasculature. Starting an agent that targets pathogenesis of PAH may prevent heart failure and the need for complicated parenteral therapies and lung transplant. Exhibit 5 shows some additional antiproliferative therapies which will be the future of PAH treatment.

Conclusion

PAH remains challenging to diagnose and requires comprehensive assessment, including right heart catheterization. Risk assessment is critical for determining prognosis, making treatment decisions, and monitoring longitudinally. The current treatment goal for PAH is to achieve low-risk status with a standard approach of upfront combination therapy with potential escalation to triple therapy, often with an agent from the prostacyclin class. Antiproliferative therapies will heavily shape the future of PAH therapies.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Chronic Lymphocytic Leukemia

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Summary

Targeted therapies have greatly improved survival outcomes for patients with chronic lymphocytic leukemia (CLL). The shift from chemoimmunotherapy to primarily oral targeted regimens has occurred for almost all patients.

Key Points

- Current first-line treatment options are BTK inhibitors until disease progression or intolerance, or fixed duration venetoclax therapy.
- Acalabrutinib, zanubrutinib, and pirtobrutinib are better tolerated than ibrutinib.
- Fixed duration ibrutinib and venetoclax is an all oral, limited duration, regimen showing superior results for sustained disease remissions.

CLL IS THE MOST COMMON ADULT leukemia in the United States (U.S.) but only accounts for 1.2 percent of all cancers diagnosed annually. The American Cancer Society's estimates for 2023 are 18,740 new cases of CLL and 4,490 deaths from CLL.[1] The five-year relative survival rate for CLL is 88 percent and there are about 200,000 people living with CLL in the U.S.[2] The median age at diagnosis is 70 years and CLL is more common in men. There are several risk factors for development of CLL (Exhibit 1).[3] However, some people who develop CLL have no risk factors whereas other people with multiple risk factors never develop the disease.

Clinically, CLL can result in constitutional symptoms (fever, chills, night sweats, weight loss, extreme fatigue), lymphadenopathy, splenomegaly, hepatomegaly, cytopenias, and/or hypogammaglobulinemia. Often, people are diagnosed with CLL when an unexplained elevated white blood cell count is found during a blood test done for another reason. About 80 percent of people have no symptoms at the time of diagnosis.

The diagnosis of CLL is made based on immunophenotyping of peripheral blood lymphocytes. Technically, CLL is a neoplasm composed of monomorphic small mature B cells that coexpress CD5 and CD23 and the diagnosis requires a $\geq 5x10^9$/L clonal B cell count. As part of the diagnostic work-up, patients are staged into low-, intermediate-, or high-risk for death prognostic groups based on how well their bone marrow is functioning. Molecular cytogenetics are also done and are used for prognosis and treatment selection. Mutations of importance include 17p13 deletion (TP53) and immunoglobulin heavy chain variable region (IGHV). About 80 percent of newly diagnosed CLL patients will have cytogenetic defects.

Patients with CLL only need treatment once they meet criteria for active disease or have significant disease-related symptoms, such as severe fatigue, drenching night sweats, unintentional weight loss (≥ 10% in previous 6 months), or fever without infection. The National Comprehensive Cancer Network

Exhibit 1: Risk Factors Associated with Development of CLL[3]

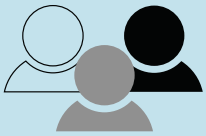
Family History

- Higher risk with first-degree relatives (parents, siblings, or children) of patients with CLL.

Exposure to Certain Chemicals

Higher risk with exposure to:

- Agent orange
- Benzene
- Chemotherapy drugs
- Pesticides (possibly)
- Radon
- Radiation



Race/Ethnicity

- Higher risk with European ancestry.
- Reduced risk with Asian ancestry.
- Differences in risk are likely due to genetics rather than environmental factors.

Age or Gender

Higher risk if:

- Older age (90% of CLL cases are in adults > 50 years old)
- Male

(NCCN) Guidelines list threatened end-organ function; progressive, symptomatic, or bulky disease (spleen > 6 cm below costal margin, lymph nodes >10 cm); progressive thrombocytopenia; progressive anemia; or steroid-refractory autoimmune cytopenias as other indications for treatment.[4]

Targeted treatments have been developed which alter B cell receptor signaling which drives CLL cell survival. Oral Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib), an oral B cell lymphoma 2 inhibitor (venetoclax), and injectable anti-CD20 monoclonal antibodies (e.g., obinutuzumab) are the targeted options for first-line treatment of CLL. The NCCN Guidelines recommend first-line therapy based on patient factors, IGHV mutation status, and cytogenetics (Exhibit 2).[4] The two main treatment options are oral BTK inhibitors until intolerance or disease progression or limited duration therapy with venetoclax and obinutuzumab. Patient preference will play a role in this choice. Importantly, targeted therapy does not cure CLL but can control it for many years. It should also be noted that chemoimmunotherapy regimens are still an option for younger healthier patients who have IGHV mutation, however, for all other patients, the oral targeted regimens have supplanted chemoimmunotherapy due to better survival outcomes.

The NCCN Guidelines include ibrutinib as *other recommended agent* because of its adverse event profile.[4] Ibrutinib has good long-term efficacy supported by multiple Phase III trials as well as data for efficacy in del17p/TP53. It has progression-free survival (PFS) and overall survival (OS) benefits out to eight years but causes higher rates of atrial fibrillation, bleeding, and therapy discontinuation for adverse events compared to the second generation agents.[5-8] An interesting analysis of data from three Phase III trials with ibrutinib found, that for patients who were aged 65 years or older when started on ibrutinib, the estimated OS rate at eight years was comparable between ibrutinib (78%) and an age-matched general population without CLL (77%).[9]

Acalabrutinib and zanubrutinib also have good efficacy data for first-line use. A comparison trial of acalabrutinib versus ibrutinib (Elevate RR) in relapsed/refractory CLL found the two agents noninferior with a median PFS of 38.4 months in both arms.[7] All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; $p = .02$) and median OS was not reached in either arm. Zanubrutinib has also been compared to ibrutinib in relapsed/refractory CLL. At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to PFS (hazard ratio for disease progression or death, 0.65; $p = 0.002$).[8] A lower rate of atrial fibrillation/flutter was observed with zanubrutinib (2.5% versus 10.1%; $p = .0014$) and major bleeding rates were also lower (2.9% versus 3.9%), as were adverse events leading to treatment discontinuation (7.8% versus 13.0%, respectively) or death (3.9% versus 5.8%). Of note,

Exhibit 2: NCCN Recommended First-Line Regimens for Treatment-Naïve CLL[4]

Type	Preferred First-Line	Selected Other Options
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Zanubrutinib	Ibrutinib Ibrutinib + venetoclax (category 2B)
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (category 1) Venetoclax+ obinutuzumab (category 1) Zanubrutinib (category 1)	Ibrutinib (category 1) Ibrutinib + venetoclax (category 2B) FCR (fludarabine, cyclophosphamide, rituximab) – consider for IGHV-mutated CLL in patients age < 65 years without significant comorbidities.

neutropenia occurred more often with zanubrutinib (28.4% versus 21.7%).

Resistance to the current covalent BTK inhibitors occurs in many patients over the course of treatment primarily due to BTK C481 mutation development.[10] These mutations prevent covalent BTK inhibitors from effective target inhibition. Third generation noncovalent BTK inhibitors such as the newly FDA-approved pirtobrutinib are an option for BTK inhibitor resistance or intolerance.[4] Pirtobrutinib was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including another BTK inhibitor in January 2023, and for CLL in December 2023. Atrial fibrillation, hypertension, and bruising (common adverse events with less specific BTK inhibitors) occur at low rates with pirtobrutinib.

Fixed duration therapy with obinutuzumab and venetoclax produces great efficacy with deep remission responses. Venetoclax regimens are typically given for up to two years and patients are observed for relapse and retreatment indications. Venetoclax-based approaches demonstrate high rates of undetectable minimal residual disease (uMRD) (75%).[11] Optimal duration of therapy remains unclear but optimizing uMRD before stopping should be the goal.

The next iteration of CLL therapy is an initial combination of a BTK inhibitor and venetoclax. Rationale for the combination are non-overlapping mechanisms of action, non-overlapping toxicity profile, and they act on CLL cells in different compartments. One trial of ibrutinib plus venetoclax therapy for 24 cycles in previously untreated patients with CLL found durable remissions over a follow-up of more than three years, with activity seen across high-risk disease subgroups.[12] With combined treatment, the proportions of patients who had complete remission (with or without normal blood count recovery) and remission with uMRD increased over time. After 12 cycles of combined treatment, 88 percent of the patients had complete remission or complete remission with incomplete count recovery, and 61 percent had remission with uMRD. This combination is included in the NCCN Guidelines as a Category 2B recommendation until more survival data are available.[4] This combination is a limited duration therapy with high rates of remission which avoids potential long-term financial and adverse event concerns with extended use of BTK inhibitors. Numerous triple therapy trials of BTK inhibitors, venetoclax, and anti-CD20 antibodies in various combinations are ongoing but for now the benefits are unknown.

Conclusion

When CLL requires treatment, patient preferences for therapy should be taken into consideration to individualize therapy. There are great options for front-line treatment – long-term therapy until disease progression or fixed duration therapy. For long-term therapy, ibrutinib has good long-term efficacy supported by multiple Phase III trials as well

data for efficacy in del17p/TP53 but causes more discontinuation due to adverse events. Acalabrutinib and zanubrutinib have excellent efficacy data with better tolerability. Pirtobrutinib is a new alternative for BTK resistance. For fixed duration therapy, obinutuzumab and venetoclax produce great efficacy with deep remission responses.

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Transforming Management Strategies by Integrating Biosimilars into the Treatment Landscape

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For a CME/CEU version of this article, please go to
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Summary

The growing availability of biosimilars is challenging payers to develop management strategies. This is especially true for adalimumab where there are now eight different biosimilars on the market and more to come. Maximizing use of biosimilars will require educational and administrative actions.

Key Points

- Numerous biosimilars are now approved in the United States (U.S.) and are on the market, with more under FDA review and many more under development.
- For agents like adalimumab where there are multiple biosimilars, payers will have to determine how to manage these and maximize use.

A BIOSIMILAR IS A BIOLOGIC PRODUCT which is "highly similar" to a reference product (original FDA-approved biologic). Exhibit 1 includes important terminology related to biosimilars.[1] The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in characterizing and manufacturing biosimilars that often do not exist in the development of small molecule drugs.[2] Thus, biosimilars are not exact copies of the originator due to necessary differences in manufacturing but the differences are not clinically significant in terms of efficacy and safety. Exhibit 2 illustrates key differences between a biosimilar and a generic small molecule medication.[1] There are key differences in molecular structure, the FDA-approval process, and development costs. Overall, a biosimilar is not a generic.

The biosimilar development process also differs from small molecule development. To demonstrate similarity, the biosimilar sponsor submits evidence from extensive structural and functional comparability assessment and pharmacokinetic and pharmacodynamic studies that the candidate biosimilar is not significantly different from the reference product.[3] The clinical efficacy and safety of the biologic molecule has already been demonstrated by the reference product, thus the goal is not to replicate unnecessary clinical trials but to use smaller-scale direct comparisons and extrapolation. The process of biologic and biosimilars approval is through the Public Health Service Act instead of the Food, Drug, and Cosmetics Act which outlines the approval process for small molecule medications. The determination of no clinically meaningful differences is based on targeted clinical trials in a sensitive population (i.e., the indication for which a difference is likely to be detected). Clinical trials are designed to establish statistical evidence that the proposed product is neither inferior nor superior to the reference product, by more than a specified margin. When a biosimilar is approved, there should be an expectation that there will be no differences in safety and efficacy.

The Biologics Price Competition and Innovation Act (BPCIA) which ushered in the biosimilar era was signed into law in 2010 and the first product was approved in 2015. Because of the high stakes

Exhibit 1: Biosimilar Terminology[1]

Biologic	A therapeutic antibody, vaccine, virus, blood product, or protein used for treatment in patients.
Biosimilar	A biologic product that is "highly similar" to the reference product, notwithstanding minor differences in clinically inactive components. There are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.
Reference Product	The single FDA-approved biologic product against which a biosimilar is evaluated.
Interchangeable	The biosimilar that would be expected to produce the same clinical result as the reference product in any given patient. For a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy or alternating or switching between the use of the product and its referenced product is not greater than the risk of using the reference product without such alternation or switch.
Extrapolation	The process of granting one or mor clinical indications to a drug without conducting new clinical and/or safety studies to support the additional indications.
Immunogenicity	Ability of a substance to provoke an immune response. In the case of a biologic or biosimilar agent, it is the ability of the drug to provoke an immune response to itself.

involved there was considerable objection to biosimilars initially.[4] There was a citizen petition to the FDA that the biologic approval process constituted an unlawful taking of private property (trade secrets) and multiple petitions requested that biosimilar product labeling should have a declaration acknowledging that a biosimilar is different from the reference product. Additionally, extended lobbying efforts were aimed at getting state legislatures to preemptively ban interchangeable biosimilars similar to bans in some states on narrow therapeutic window medication automatic interchange. Multiple patent infringement lawsuits were also filed. Ultimately large biologic manufacturers moved the needle by becoming producers of biosimilars.

The FDA has taken actions to improve biosimilar acceptance. FDA actions include working to improve efficiency and predictability in the biosimilar and interchangeable product development and review process, guidance on the FDA-evaluation process and data recommendations, such as product-specific and other scientific guidance, and the creation of review templates specifically for 351(k) Biologics License Applications (BLAs).[5] It has also increased communications with stakeholders regarding the development, review, and approval of biosimilar and interchangeable products and taken a more proactive role to educate clinicians, patients, and payors about biosimilar and interchangeable products. The FDA has also evaluated whether manufacturers are inappropriately delaying the approval of biosimilar or interchangeable competitors. Despite the initial resistance, the biosimilar market has significantly increased in the last five years. There are currently 45 approved biosimilars of 14 reference products in the U.S., seven of which were approved in 2022 and five in 2023 (as of December 9, 2023).[6,7]

There is only one reference product, etanercept (Enbrel®), for which biosimilars have been approved but have not yet launched, due to litigations resulting in injunctions until the time of patent expiration (2029).[8] Of the biosimilars so far approved by the FDA, and for those in development, all but a few are owned by the larger pharmaceutical companies.[9] Market share growth varies widely by product and indication. Familiarity of biosimilars among key specialty providers (rheumatology, gastroenterology, dermatology, ophthalmology) is significant.[10] Biosimilar sales over the next five years are expected to total $80 billion, ranging from $53 billion to $105 billion depending on volume uptake and pricing discounts.[9]

One legal issue limiting biosimilar use is state interchangeability law which varies widely across the U.S. Interchangeable products can be substituted by pharmacists without contacting the original

Exhibit 2: Comparison of a Biosimilar To Generics[1]

	Generics	Biosimilars
Molecular structure	Simple structure; low molecular weight.	Complex structure; large molecular weight proteins.
	Can create identical copies.	Minor variations in molecular composition may occur; this can also occur from lot to lot with reference biologics.
FDA approval process	No clinical efficacy trials required for approval; focus on pharmacokinetics.	Clinical trials necessary.
	When approved, all indications apply.	Manufacturers must apply for extrapolation. across indications.
	Substitution directed by Orange Book.	Substitution directed by Purple Book.
Healthcare costs	Costs to bring to market relatively low.	Costs to bring to market very high.

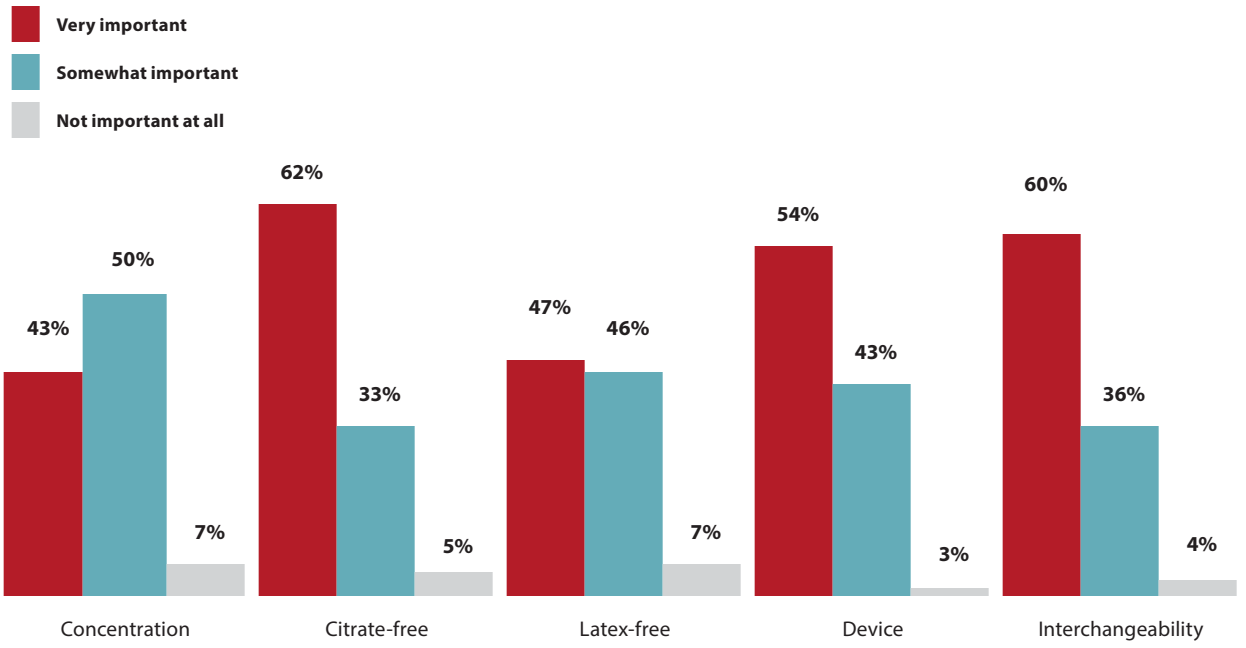
Exhibit 3: Inconsistent Regulations by State[11]

Alabama	Requires express prescriber permission to substitute, cannot substitute at all to Medicaid recipient if originator product is lower in net cost after rebates.
Arkansas, North Carolina, Ohio	Can substitute without prescriber approval only if substituted product is lower cost to the patient.
California	Can substitute only if biosimilar is designated interchangeable and biosimilar does not increase cost to patient.
Vermont	Pharmacist must select lowest priced interchangeable product unless otherwise instructed by 1) the provider or 2) the patient if the patient agrees to pay additional costs in excess of the benefits provided by the patient's health benefit plan.

prescriber. Most states have expressly adopted the federal definition of biosimilar interchangeability. Some states also permit substitutions for biosimilars listed as therapeutically equivalent in the Orange Book. Some states maintain their own list of interchangeable biosimilars. Exhibit 3 gives examples of the inconsistency in state regulations.[11] FDA interchangeable designation of biosimilars have been limited, with seven approved interchangeable biosimilars of four reference products to date.[6,7] Interchangeability approval requires data showing no change in efficacy or safety with switching between products. Manufacturers conduct switch studies in which patients alternate between the reference product and the interchangeable biosimilar and compare those patients to patients who are only being treated with the reference product.

Legal disputes over biosimilar approvals remain common in 2023 as reference product manufacturers seek to maintain their market exclusivity. There are a variety of ways patent disputes proceed in the U.S., including *inter partes*

Exhibit 4: Physician Perceptions of Adalimumab Biosimilar Requirements[10]



review (IPR) and post-grant review (PGR) at the United States Patent and Trademark Office, and litigation under the BPCIA. As of February 28, 2023, there have been 144 biosimilar-related IPRs encompassing 70 patents and 14 reference products, and there have been 46 BPCIA litigations related to 12 reference products.[12] PGRs have not been a preferred way of resolving biosimilar-related patent disputes, with only three biosimilar-related PGR filings to date. While biosimilar growth will continue to accelerate, inconsistencies in the legal and regulatory environment create significant issues for all stakeholders. Pharmacists and physicians need education in the regulatory environment. Payers need to understand the evolving regulatory environment. There may be patient confusion as the biosimilar options grow.

Payers have a major focus on immunomodulators and the possibility of savings with biosimilars. Spending on new and existing autoimmune products exceeded any other therapeutic area, reaching $42 billion over the past five years.[13] Some changes in the immunomodulator biosimilar landscape occurred in 2023 and more are expected in the coming years. The first adalimumab biosimilar, adalimumab-atto, launched in January 2023. Adalimumab-atto was also the first adalimumab biosimilar to receive FDA approval in September 2016. Following adalimumab-atto, seven other adalimumab biosimilars were launched in 2023 (adalimumab-adbm, adalimumab-bwwd, adalimumab-fkjp, adalimumab-adaz, adalimumab-aqvh, adalimumab-aacf, adalimumab-afzb). An additional adalimumab biosimilar (AVT02) is awaiting FDA approval. With all these options, the impact on rheumatology patients, their providers, and office staff will be profound. In one survey of rheumatologists, 47 percent said they were either very excited or excited about the growing number of rheumatology biosimilars anticipated to come to market whereas 33 percent were neutral and 20 percent disagreed.[10]

It is still not clear what the role of interchangeability will be in key stakeholders' decision-making especially where there are numerous options as with adalimumab. A big concern surrounding the designation is that interchangeable biosimilars may be viewed as superior to biosimilars that do not have interchangeability designation.[10]

Interchangeable biosimilars are not better or safer than any other biosimilars for the same originator.

Exhibit 5: Different Stakeholders Have Different Goals

Patients	Payers	Providers	Biosimilar Companies
Less out-of-pocket costs influenced by biosimilar coverage options.	Favorable net price and contract for optimal formulary coverage will increase use.	Patient acceptance, compliance, and persistence with biosimilar.	Hopefully return on investment and continued development encouragement
Broader medication insurance coverage.	Interchangeability a relatively new aspect.	Ease to prescribe including payer coverage.	Cost versus benefit of interchangeability.
Similar attributes and services when compared to innovator.		Incentives for biosimilar prescribing.	

The designation only means that switching studies have been conducted and that it can be supplied more easily to patients. The influence that the interchangeable designation will or will not have on payer formulary coverage, provider prescribing, patient acceptance, and regulations in individual states, is not yet known.

Using adalimumab as an example, only one biosimilar product currently has an interchangeable designation but several have applied to the FDA for the designation. As shown in Exhibit 4, of rheumatologists surveyed, interchangeability is one of the most important attributes but other factors also impact selection.[10] Beyond interchangeability, cost savings are important to payers and patients. Price declines for biosimilars range significantly but appear to reflect prior assumptions of 30 percent discounts, though higher discounts have occurred and are possible in the future.[10] One of the key features which also impacts selection among adalimumab biosimilars is the concentration of the product. High-concentration formulations allow for patients to receive fewer doses of adalimumab compared with low-concentration formulations but currently no high-concentration biosimilars are designated as interchangeable. One survey found that cost, payer placement, interchangeability, formulation concentration, and ease of use of autoinjectors will drive adalimumab biosimilar uptake in that rank order.[14]

To increase prescribing of biosimilars, prescriber education will be needed. In the rheumatologist survey previously discussed, those surveyed had concerns about efficacy, lack of cost benefit, how to evaluate and when to prescribe a biosimilar versus reference product.[10]

The multiple stakeholders all have something to gain as the biosimilar market grows and competition increases (Exhibit 5). Payers are likely to see the greatest financial benefits from biosimilars and are at the forefront of decision-making around biosimilars. This is because they will oversee formulary lists and manage policies, such as step therapy and prior authorization requirements, that impact whether patients will have access to biosimilars. There are many important considerations in addition to cost that need to be considered when evaluating biosimilars. It is important that payors consider the impact of state laws regarding substitution, including how interchangeable and noninterchangeable biosimilars may be used. All influencers (payers, prescribers, patients, pharmacies, and manufacturers) have a role in the optimization of biosimilar use. Different pharmacy distribution models (i.e., retail, mail, specialty) have different abilities to communicate with, assist, and influence prescribers in selecting biosimilars.

Payers are likely to gain experience and learn in real time as the biosimilar market continues to evolve over the next 12 to 15 months. With the adalimumab biosimilars, payers will likely structure formularies using one of three strategies – preferring the reference product, preferring at least one biosimilar, or covering the biosimilar(s) and reference product at parity. In terms of savings with biosimilars, a report from the Health and Human Services Office of Inspector General found that Medicare Part D plans alone missed out on between $84 million and $143 million in savings during 2019 by prioritizing reference products over biosimilars.[15] Some industry experts have called for a parity approach, which could allow for providers to pick the right product for their patients based on price, availability, and patient preference.[14] Others have argued that preferring biosimilars is the best way to ensure biosimilar utilization and savings for all stakeholders. Payers will need to evaluate which strategy is best for their organization, considering

the needs of all their stakeholders.

Numerous options can be instituted to encourage the use of biosimilars. Payers can consider a dedicated specialty tier for generics and biosimilars, increasing add-on payments to providers who use biosimilars (e.g. ASP plus 8% versus 6%), a shared savings program to encourage biosimilar adoption, educational programs for prescribers focusing on evidence from studies in which patients switched to biosimilars, real-world evidence from post-marketing studies, and streamlined administrative and prior authorization process for biosimilars.[16]

Payers may want to look at European experiences. The European Union and the United Kingdom have used biosimilars a decade longer than the U.S. As a result, these areas have become major subjects of study on how to manage growing biosimilar markets, generate healthcare savings, instill competition and innovation, and collect real-world data. The European Union has 10 adalimumab biosimilars authorized for marketing, all of which were made available to patients shortly after approval, and do not have an interchangeability designation. Biosimilars offered at the pharmacy level can be substituted for a reference product without having to receive permission from a physician, and clinical outcomes have not suffered as a result.[17]

Conclusion

The biosimilar market is exploding with numerous approvals in the U.S., and many more under FDA review and development. For agents like adalimumab, where there are multiple biosimilars, payers will have to determine how to manage these and maximize use.

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Achieving Treatment Goals for Inflammatory Bowel Disease: New Evidence and Updates to Guide Treatment Plans

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Summary

There are numerous treatment options for inflammatory bowel disease (IBD) but choosing among them can be challenging. The management guidelines for IBD which assist clinicians in choosing therapy are evolving and sometimes are not up-to-date with the many on-going changes.

Key Points

- Guidelines on management of IBD focus on treating the disease based on severity of disease and using biologics early for moderate-to-severe disease without step therapy.
- Medication is selected based on patient preferences, disease severity, and adverse events.
- Importantly, oral administration does not equal safer than infusion or self-injection.
- Short-term targets of treatments are symptomatic response, remission, and biomarker normalization.
- A multidisciplinary care team is optimal for long-term management.

INFLAMMATORY BOWEL DISEASE (IBD) is a long-term relapsing and remitting disorder which includes ulcerative colitis (UC) and Crohn's disease (CD). There are numerous treatment guidelines published by both the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) (Exhibit 1).[1,2] Overall, the guidelines on management of IBD focus on treating the disease based on severity of the disease. Biologics should be selected early for moderate-to-severe disease and there is no role for step therapy.

The most recent guideline is the AGA role of biomarkers in UC. In a symptom-free remission, the guideline suggests a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone, to identify ongoing but asymptomatic disease.[3] If fecal calprotectin or lactoferrin are monitored every six to 12 months, disease flares can be prevented. Thus, the guidelines recommend this monitoring. Fecal calprotectin should be less than 150 µg/g, lactoferrin normal, or C-reactive protein (CRP) normal to rule out inflammation and avoid routine endoscopic assessment of disease activity. CRP is nonspecific so the other two are preferred. Endoscopic evaluation should be done when biomarkers indicate inflammation in the asymptomatic rather than empiric treatment adjustment.

In those with symptomatic UC despite treatment, the biomarker guidelines suggest checking biomarkers and symptoms.[3] Elevated biomarkers and moderate-to-severe symptoms indicate active inflammation and inform treatment decisions without the need for routine endoscopic evaluation. Endoscopic evaluation is suggested in patients with elevated biomarkers and mild symptoms or normal biomarkers and mild symptoms. With these biomarker guidelines, payers will see greater use of biomarkers, which should be covered, and

Exhibit 1: American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) guidelines[1,2]

- ACG Clinical Guideline: Management of Crohn's Disease in Adults – 2018
- ACG Clinical Guideline: Ulcerative Colitis in Adults - 2019
- AGA The role of biomarkers for the management of ulcerative colitis – 2023
- AGA Medical management of moderate-to-severe luminal and perianal fistulizing Crohn's disease 2021
- AGA Management of moderate-to-severe ulcerative colitis 2020
- AGA Role of probiotics in the management of GI disorders 2020
- AGA Management of mild-to-moderate ulcerative colitis 2018
- AGA Therapeutic drug monitoring in inflammatory bowel disease 2017
- AGA Management of Crohn's disease after surgical resection 2016

Exhibit 2: Challenges When Selecting a Biologic

Different classes of biologics	• Which subtype will a patient respond to best • Lack of testing to assess how the immune system is activated • Limited head-to-head trials/comparative effectiveness trials • Most studies evaluate patients with sequential failures
Patient preference	• Patient values hierarchy: efficacy, safety, convenience • Most study outcomes are response and remission but lack quality of life assessment
Severity of disease **Disease subtype**	• Inpatient versus Outpatient • Rapidly progressive/evolving disease • UC versus CD (e.g. fistulizing disease)
Insurance approvals	• Prior authorizations • Step therapy • Home infusions
Physician experience/knowledge	• Evolving evidence • New drugs • Practice changes

fewer endoscopic procedures. The combination of increased biomarker use and fewer procedures should improve patient outcomes and reduce costs.

The AGA Medical Management Guidelines for moderate-to-severe luminal and perianal fistulizing CD and moderate-to-severe UC reinforce the notion that moderate-to-severe disease should be treated with biologics and that step therapy has no place in the management of moderate-to-severe disease because the lower level therapies (thiopurines, 5-aminosalicylates, corticosteroids, and some tumor necrosis factor antagonists) are not effective.[4,5] Also, which medication is most effective in CD or UC varies and data from head-to-head trials are beginning to provide evidence for better therapy selection. Evidence-based practice is to personalize therapy

Exhibit 3: Important Biologic Information[6,7]

Anti – Tumor Necrosis Factor (TNF)

- Consider therapeutic drug monitoring when starting therapy
- Up to one-third of patients may not respond
- Antibody formation/loss of response in up to 40% of patients
- **Infliximab**

  Most efficacious and should be considered in severe disease
- **Adalimumab**

  Less efficacious in UC

  Should be dosed based on weight
- **Certolizumab**

  Limited to no role for induction of remission in CD due to lack of efficacy and no role for UC

Anti-integrin

- **Natalizumab**

  Rarely used given risk of PML in patients JC virus positive

  AGA recommends against its use
- **Vedolizumab**

  Gut specific α4β7

  Safest biologic

  Consider in individuals with more comorbidities

  Consider in patients with concomitant PSC (no risk of drug-related LFT elevation)

  Ideal role for moderate disease in UC

  Might consider slightly lower for CD due to lower efficacy

  Lower risk of immunogenicity < 10%

  Subcutaneous self-administered formulation now available

Anti-interleukin

- Safety very close to vedolizumab
- Convenience of every eight-week dosing
- Improved bioavailability with weight-based IV dosing to start, then switch to self-injection
- Remission rates greater than 50%
- **Ustekinumab - IL12/23 inhibitor**

  Efficacy on par with anti-TNF

  Lower risk of immunogenicity < 10%

  Effective for UC and CD
- **Risankizumab - IL 23 inhibitor of the p19 subunit**

  More targeted therapy

  Dosing 3 infusions (week 0, 4, 8) then subcutaneous at week 12 and then every 8 weeks

  Might consider in someone with some response to ustekinumab but not complete response
- **Mirikizumab - IL 23 inhibitor of the p19 subunit**

  Similar to and same dosing as risankizumab

  Newest biologic (October 2023)

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Janus Kinase (JAK) Inhibitors

- Oral agent small molecules with no immunogenicity
- Black box warning against use as a first-line agent, must fail anti-TNF first
- Lower dose after 8 weeks
- **Tofacitinib**

  Approved only for UC; failed Phase II study in CD

  Jak 1 and Jak 3 inhibition

  High dose > 8-week risk of pulmonary emboli and sudden death

  Highest risks of side events (infection, zoster, elevated lipid panel)
- **Upadacitinib**

  Approved for UC and CD

  Selective Jak 1 inhibition

  No data to suggest pulmonary emboli or sudden death risk but still has black box warning

  Appears to have a low risk of adverse events but still questions about long-term risk

S1P antagonist

- New class of oral agents for UC (also approved for multiple sclerosis)
- Works by blocking lymphocytes from leaving the spleen and lymph nodes into circulation that trigger inflammation in IBD
- No immunogenicity
- **Ozanimod**

  S1P1 and S1P5 receptor antagonist

  Efficacy data suggests best for moderate rather than severe disease

  Baseline testing issues, adverse events, and contraindications limit the use of this agent for UC

  Baseline testing: CBC with differential, LFTs, ECG, ophthalmologic exam (if history of uveitis, macular edema or diabetes),

  varicella antibodies, pulmonary function if underlying pulmonary disease

  Adverse events

  Bradycardia, conduction delays, herpes zoster, infection, macular edema, decline in pulmonary function

  Contraindications

  History of myocardial infarction, unstable angina, decompensated heart failure, heart block), severe sleep apnea, transient ischemic attack, Drug interactions, pregnancy (teratogenic)

UC = ulcerative colitis; CD = Chron's disease; AGA = American Gastroenterological Association; PML = progressive multifocal leukoencephalopathy; JC = John Cunningham; PSC = primary sclerosing cholangitis ; S1P = Sphingosine-1-phosphate

with the best medication to control the degree of inflammation that a patient has and payer policies should reflect this evidence. There are still many payer policies which require, step therapy, failure of certain classes, and delay of effective therapy, all of which can lead to disease complications.

Biologics are the main treatment of IBD but because there are many different classes approved for treating UC and CD, choosing an agent can be difficult. Monoclonal antibodies against tumor necrosis factor (TNF), the interleukin (IL) 12 and 23, the α4β7 integrin, and Janus Kinase (JAK) inhibitors, and sphingosine-1-phosphate (S1P) antagonists are available. Exhibit 2 outlines some of the challenges when selecting a biologic.

Patient preference needs to be a key part in treatment selection but clinicians and patients may have different preferences. For example, clinicians

may want to select the most efficacious agent which has a higher risk of adverse events but the patient is not willing to take the same risk. A patient may want to be on vedolizumab because it is the safest agent but with that choice, they give up some convenience as it is an infused agent rather than self-administered.

The various biologics available for treating IBD target various parts of the immune system and thus have different efficacies and adverse events. Exhibit 3 covers some important information to know about and incorporate into payer policies for the biologics used to manage IBD.[6,7] Although patients may be excited to know there are now oral medications for IBD, both the JAK inhibitors and the S1P antagonist ozanimod cause some significant adverse events and are not necessarily more safe than injectable agents. Future generations of JAK and S1P antagonists will be more specific and hopefully will have fewer adverse events and contraindications.

The future of IBD treatment is a personalized approach aimed at identifying which patient should be treated with a specific drug at a precise time point. Personalized medicine has the advantage of improving efficacy of the drug and limiting adverse reactions, thereby improving the quality of life of patients, and reducing costs. Immunologic tests to identify which immune pathway is active to better select which biologic, or small molecule agent, are needed because up to 30 percent of patients are non-responders to biologics. Current precision-medicine tests for IBD are lacking but numerous tests are under investigation.[8] Transcriptomics is colonic mucosal gene profiling to predict response to therapy. Molecular endoscopy uses fluorescent antibodies sprayed onto mucosa and confocal laser endomicroscopy to detect and quantify mucosal TNF cells to predict response to anti-TNF biologics. Genetic variants may be more likely to respond to certain therapies so identification of these variants is needed. Serum concentrations of interleukins may predict response to interleukin therapy. Lastly, the gut microbiome diversity and certain bacterial species may predict response to therapy. Eventually, there will be a panel of biomarkers, which can be checked before starting any therapy, from which to select the most appropriate agent.

Another future advance is the use of biologic/small molecule combinations since the various classes target different areas of immune system.[9] There are definitely safety issues with targeting multiple immune system mechanisms. There are also efficacy and policy issues with combination therapy. Meta-analysis cohort studies or case series (> 10 patients) reporting the safety and effectiveness of simultaneous use of biologic agents in combination or with tofacitinib in patients with IBD found possible benefit in selected patients.[10] The most common combinations included TNF antagonists and vedolizumab (48%) and ustekinumab and vedolizumab (19%). Sixty-one percent of patients had previously failed at least one of the two therapies used in combination. The main indications for dual therapy included medically refractory IBD (81%) and concurrent extra-intestinal manifestations or rheumatologic disease (12%). Seventy-six percent of the included patients had CD. In clinical practice, the most common combination is vedolizumab and ustekinumab to minimize adverse events. One way to use combinations is in those with a severe flare and then attempt at tapering to one agent at remission.

More targeted therapies for IBD are on the horizon. Additional JAK inhibitors such as filgotinib, brepocitinib, and ritlecitinib (already approved for alopecia areata) are under investigation for IBD.[11] Carotegrast methyl, an oral agent, exerts an anti-inflammatory effect by blocking the interaction of α4β1 or α4β7 integrins and their ligands thereby inhibiting the adhesion of inflammatory cells, including T cells, to vascular endothelial cells and extravasation into inflammatory sites. It has been approved in Japan for moderate UC and is currently in trials in the United States (U.S.).[12] Several other classes of agents are also under investigation.

A last area to discuss is how to achieve the treat-to-target goals of IBD therapy. Treat-to-target in IBD means achieving the short-term goals of clinical response (symptomatic and mucosal healing by endoscopy) and clinical remission. Additional long-term outcomes are normal growth in children with IBD, absence of disability related to the disease, and normalized quality of life. To achieve these outcomes, therapy needs to be optimized with therapeutic drug monitoring, stool biomarkers as previously discussed, radiologic evaluation, and endoscopic evaluation. Therapy can be optimized by ensuring patients take their medication and continue taking it (adherence and persistence). One way to optimize patient experience and outcomes while decreasing healthcare expenses is the specialty medical home (SMH), which provides multidisciplinary, high-quality care for IBD.[13] A team-based approach brings everything needed to the patient without duplication of services. Team members include gastroenterologists, primary care, rheumatology, dermatology, mental health, home health, pathology, pharmacists, and many more. Coordinating care through a medical neighborhood is another approach which means not every team member needs to be under the same roof but are interconnected through technology.

Conclusion

Guidelines on management of IBD focus on treating the disease based on severity of disease, selecting biologics early for moderate-to-severe disease, while avoiding step therapy. Multiple classes of biologics and small molecules are available. Clinicians should select medication based on patient preferences, disease severity, and adverse events. Importantly, oral administration does not equal safer therapy. Short-term treatment targets are symptomatic response, remission, and biomarker normalization. A multidisciplinary care team is optimal for long-term management.

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New Frontiers in the Treatment and Management of Cystic Fibrosis: Managed Care Considerations in an Evolving Treatment Paradigm

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For a CME/CEU version of this article, please go to
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Summary

Tremendous advances in the treatment of cystic fibrosis (CF) have been made since the introduction of the first disease-modifying agent in 2012. Therapies which correct the underlying pathophysiologic defect are available for over 90 percent of patients with CF. Long-term benefits of these therapies are now being shown such as, for example, a reduction in lung transplants.

Key Points

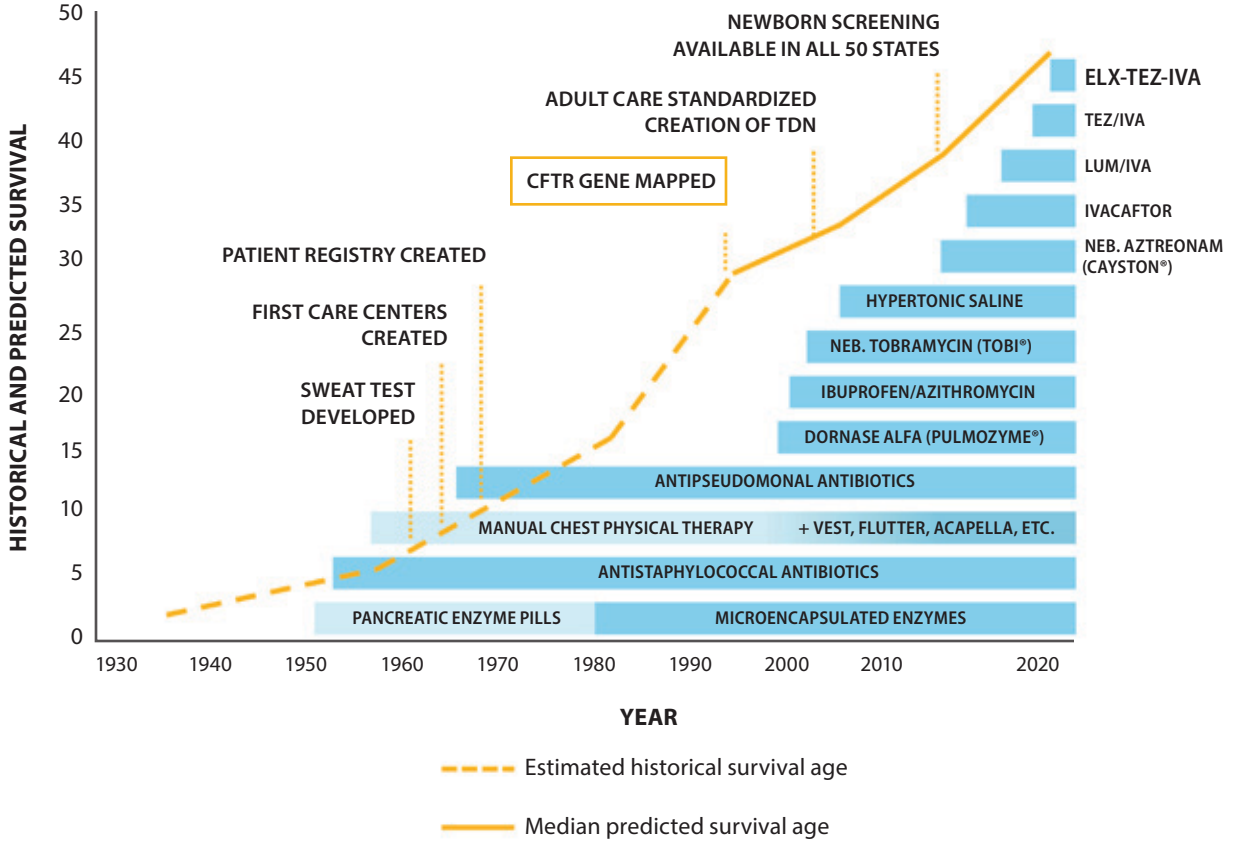
- CF causes a substantial clinical and economic burden.
- Triple therapy with two correctors and one potentiator is the standard of care for F508del homozygous or heterozygous disease.
- CFTR modulators should be started as soon as possible after diagnosis.
- CTFR modulator therapy reduces pulmonary exacerbations, lung function decline, lung transplant rates, and improves survival.

CYSTIC FIBROSIS (CF) IS A RARE, LIFE-shortening, autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF affects about 30,000 people in the United States (U.S.) and is primarily a disease of those of Northern European descent.[1] Greater than 2,000 mutations in the CFTR gene have been reported but only 25 mutations are found in the majority of patients. The dysfunctional CFTR protein produced results in thick sticky mucus that obstructs the airways and ducts of the pancreas and liver. Every organ can be impacted either primarily or secondarily by the disease.

The median survival with CF has increased from 32 years in 1995 to 1999 to 56 years in 2018 to 2022. There are now more adults living with CF than there are children with CF.[2] This improvement has come from treatments targeted at the secondary effects of CFTR dysfunction in the lung and pancreas (poor mucosal clearance, pancreatic insufficiency, infection, and inflammation) by using airway clearance techniques, nutritional support with pancreatic enzymes, inhaled and oral antibiotics, and CFTR targeted therapy. Exhibit 1 shows the benefits of various treatments over time on survival.[3] Given that the first specific CFTR targeting medications were approved in 2012, survival improvements will only continue.

Newborn screening, mandated in all 50 states, identifies most new cases of CF but there are people with CF who were born before newborn screening was mandatory who may have milder forms of the disease that has never been identified. Patients with CF diagnosed in adulthood typically present with respiratory complaints, and often have recurrent or chronic sinopulmonary disease but they may have

Exhibit 1: CF Median Survival[3]



other phenotypic features of CF (Exhibit 2).[4] It can be difficult to diagnose those who have an atypical presentation of CF.

People with CF have substantial disease and financial burden. The disease burden increases with age consistent with the progressive nature of CF.[5] Treatment burden is also high; patients can be on numerous different medications and therapies targeting various aspects of the disease.[5]

The progress in CF treatment in recent years has come from understanding and targeting the underlying pathologic mutations that occur with this disease. CFTR mutations can be categorized into five different classes which are grouped by the issues in the production of the CFTR protein (Exhibit 3).[6] The amount of functional CFTR activity is closely correlated with disease severity. Class I are protein production mutations, Class II are protein processing mutations, Class III are gating mutations, Class IV are conduction mutations, and Class V are insufficient protein mutations.[1] Class IV and V mutations are residual function mutations and those with these mutations tend to have less severe disease. The final type of mutation (Class VI) can result in a working CFTR protein but the protein configuration is not stable and will degrade too quickly once on the cell surface.

F508del, a Class II mutation that results in defective processing but also causes a gating issue, is the most common mutation in CF patients in the U.S. Because there are different problems with the CFTR protein, different therapies are needed for each problem to impact the disease. Correctors and potentiators are two ways to increase CFTR function. Correctors increase the cellular processing and delivery of CFTR proteins to the cell surface and potentiators increase the flow of ions through CFTR present on the cell surface.

The first disease-modifying agent approved for CF was ivacaftor, a potentiator. It is indicated for the treatment of CF in patients aged one month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. Ivacaftor decreases chloride content in sweat to normal values and decreases the rate of lung function

Exhibit 2: Phenotypic Features Consistent with a Diagnosis of CF[4]

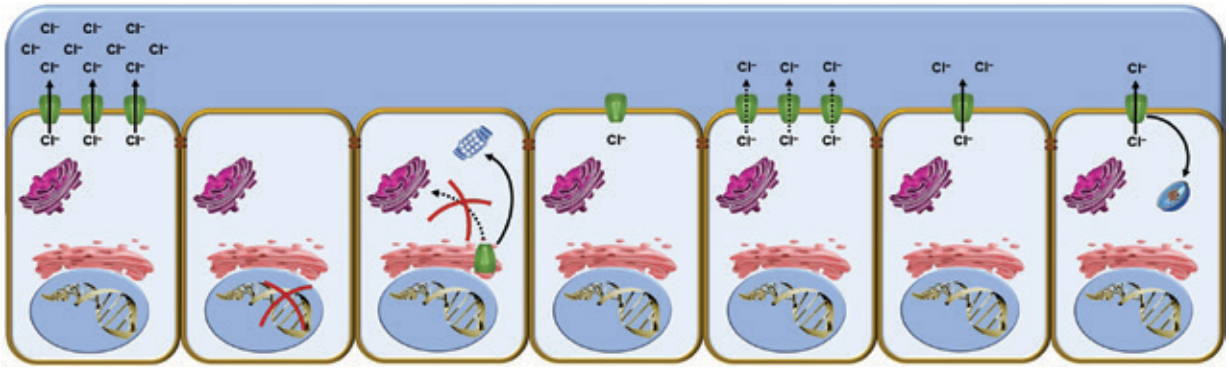
Chronic sinopulmonary disease manifested by:
Persistent colonization/infection with typical CF pathogens
Chronic cough and sputum production
Persistent radiograph abnormalities
Airway obstruction by examination of spirometry testing
Sinus disease
Digital dubbing
Pancreatic
Pancreatic insufficiency
Recurrent acute or chronic pancreatitis
Pancreatic abnormalities on imaging
Genital abnormalities in male patients
Obstructive azoospermia

decline in patients with appropriate mutations by about 50 percent.[7-11] Deterioration in lung function determines the need for lung transplant. Ivacaftor also reduces pulmonary exacerbation rates, even in those who lung function does not improve.[12]

Three correctors are FDA approved – lumacaftor, tezacaftor, and elexacaftor. These are given in combination products which also contain ivacaftor because a corrector alone does not change CFTR function sufficiently. Although the combination of a corrector and potentiator (tezacaftor/ivacaftor and lumacaftor-ivacaftor) produces satisfactory results in those with F508del mutations responsive to these agents, the majority of patients are now receiving triple therapy with two correctors and a potentiator because of improved efficacy.[2]

Triple therapy further enhances in vitro F508del CFTR function. For example, lumacaftor/ivacaftor improved CFTR function to 30 percent of normal but adding an additional corrector increases function to 50 percent of normal in those homozygous F508del. In a heterozygote with only one F508del mutation, lumacaftor/ivacaftor improved function to 15 percent of normal and the addition of the second

Exhibit 3: CFTR Mutation Classes and Treatment Approach[6]



	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation/ Correct mis-splicing	Promote protein stability

corrector improves function to 30 percent of normal.

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is indicated for patients aged two years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data and is the current standard of care for this patient population. FDA approval for use in those younger than two years of age will occur soon. Triple therapy slows reduction in lung function, reduces pulmonary exacerbations, reduces sweat chloride, and improves symptoms.[13,14]

Over 90 percent of CF patients have mutations which can be treated with ivacaftor monotherapy, dual combination, or triple combination. Benefits of reducing the need for lung transplants and annual exacerbations have already been shown with disease-modifying treatment. In the CF Foundation Patient Registry, the number of transplants in 2022 was dramatically lower than 2019 and prior years which corresponds to improvements in lung health.[2] Registry data also shows improved lung function, reduced exacerbations in both children and adults, and higher rates of pregnancy.[2] Additional benefits of CFTR modulators can include reductions in sinus disease, CF-related diabetes, liver disease, and secondary complications of renal toxicity, ototoxicity for antibiotic use, osteoporosis, depression, and anxiety. Data on these benefits should be released in the next few years.

It is important that disease-modifying therapy be started as soon as possible after diagnosis. A study using a person-level microsimulation model to estimate the survival and lifetime clinical benefits of ELX/TEZ/IVA treatment versus tezacaftor plus ivacaftor [TEZ/IVA] or lumacaftor plus ivacaftor [LUM/IVA]) or best supportive care (BSC) alone in people with CF aged 12 years and older, who are homozygous for F508del-CFTR, has been published.[15] The median projected survival for those treated with ELX/TEZ/IVA was 71.6 years which is an increase of 23.2 years versus TEZ/IVA, 26.2 years versus LUM/IVA, and 33.5 years versus BSC alone. Treatment with ELX/TEZ/IVA also reduced disease severity as well as the number of pulmonary exacerbations and lung transplants. In a scenario analysis, the median projected survival for those initiating ELX/TEZ/IVA between the ages of 12 and 17 years was 82.5 years, an increase of 45.4 years compared with BSC alone. Initiating it even earlier in life – at the time of diagnosis – should allow those with CF to achieve a near-normal life span.

Another interesting benefit of triple therapy is a possible reduction in other medications needed. The Simplify study compared discontinuing or continuing mucoactive agents (nebulized hypertonic saline and dornase alpha). In individuals with CF on ELX/TEZ/IVA with relatively well-preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for six weeks did not result in clinically meaningful differences in pulmonary function when compared with continuing treatment.[16] More data are needed before supportive therapies can be routinely discontinued but there is hope for reducing the treatment burden of CF.

There is still a need for additional disease-modifying agents. About 15 to 20 percent of patients only receive modest benefit from the current agents. Additionally, there are about 10 percent of patients who do not have a mutation targeted by the already approved agents. There are also some patients who cannot tolerate the CFTR targeted therapies.

There are other CFTR mutation-specific and independent approaches beyond CFTR modulators under study. Mutation specific therapies include gene-editing (CRISPR/Cas9) and modified transfer RNAs for nonsense mutations such as investigational EX-02 which increases full-length CFTR messenger RNA. Mutation-independent therapies include CFTR gene therapy with adeno-associated virus and nanoparticles, CFTR mRNA delivery, and stem cells. For example, MRT5005 is an investigational inhaled therapy that delivers mRNA that encodes fully functional CFTR protein to lung cells. One issue with these various gene-based therapies is the very long development timeline.

Conclusion

CF causes a substantial clinical and economic burden but triple combination therapy is producing significant short- and long-term benefits. The highly effective CFTR modulators should be started as soon as possible after diagnosis. The next iteration of CF treatment will be gene-based therapies but these have very long developmental timelines.

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Innovative Approaches in the Treatment and Management of Hereditary Angioedema: Key Considerations in Managed Care Decision-Making

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Summary

Hereditary angioedema (HAE) is a rare, potentially fatal disease which can also be very debilitating if not adequately treated. Patients require on demand medications for treatment of HAE attacks to prevent death. Short- or long-term prophylactic treatment will also be required by many patients.

Key Points

- Clinicians need to consider HAE when encountering cases of angioedema.
- HAE is mediated through bradykinin.
- Type I and II HAE result from a deficiency of C1-INH.
- HAE normal C1-INH is likely bradykinin-mediated, but definitive diagnostic tests are lacking.
- Effective treatments which reduce bradykinin production or block a bradykinin receptor are available.
- HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, and patient quality of life.

ANGIOEDEMA IS THE RESULT OF FLUID extravasation into deep dermis and subcutaneous tissues and can be mediated by bradykinin or mast-cell products such as histamine (Exhibit 1).[1] The clinical presentation of angioedema is non-pitting localized swelling in the skin or mucosa. Onset is minutes to hours and the swelling frequently has an asymmetric distribution which is not in dependent areas. The causes of angioedema are shown in Exhibit 2.[2,3]

Effective treatment relies on identifying the underlying cause, especially in life-threatening cases. Most cases result from mast-cell product release, typically from an allergic reaction, but bradykinin-mediated angioedema results in a disproportionate number of deaths compared with other types of angioedema.[4]

Hereditary angioedema (HAE) is a rare bradykinin-mediated condition characterized by the presence of angioedema without urticaria in the form of acute attacks that are sometimes preceded by prodromal symptoms.[5] It occurs in approximately one in 50,000 individuals worldwide. There are approximately 6,000 affected in the United States (U.S.).

The majority of HAE cases are caused by complement esterase inhibitor (C1-INH) gene mutations which lead to deficiency (Type 1) or dysfunction (Type 2) in C1-INH. C1-INH inhibits all active enzymes of the bradykinin-forming cascade. With a C1-INH deficiency, bradykinin

Exhibit 1: Mediators of Angioedema

Mast-cell mediated	Bradykinin-mediated
– release of mast cell mediators increase vascular permeability histamine leukotriene C4 prostaglandin D2 heparin – **~ 90% associated with urticaria and/or pruritis** – **Responds to epinephrine, antihistamines, or corticosteroids** – **Onset over minutes to hours**	– generation of bradykinin and complement-derived mediators increase vascular permeability – absence of urticaria or pruritis – Pain or burning may be present – Does not respond to epinephrine, antihistamines, or corticosteroids – Onset over hours

Exhibit 2: Causes of Angioedema[2,3]

• Allergic: Foods, drugs, insect stings/bites • Radiocontrast media • ASA and other NSAIDs • Autoimmune Diseases • ACE inhibitor-induced	• C1 inhibitor deficiency – Hereditary: Types 1 and 2 – Acquired • Hereditary with normal C1 inhibitor • Idiopathic – Histamine-induced/Mast cell-mediated – Bradykinin-induced

levels increase. Bradykinin causes endothelial cell leakage through vasodilation and increased vascular permeability. Types 1 and 2 are bradykinin mediated and several features of normal C1-INH suggest it is also bradykinin mediated.[6] Type 1 is most common accounting for 85 percent of cases; Type 2 accounts for 15 percent.[5] HAE with normal C1-INH appears to occur in less than 1 percent of HAE cases and is more common in women than in men, whereas the Type 1 and 2 occur equally in women and men.[5,7]

HAE can be quite severe, affecting the face, oropharynx (causing risk of asphyxiation), extremities, gastrointestinal system, and genitourinary tract. Depending on the location of swelling, HAE can be life-threatening or disabling. One-third of patients with HAE develop a prodromal non-itchy rash (erythema marginatum). HAE attacks increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Notably, they are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine. Attacks typically occur unpredictably and vary in frequency. The average angioedema attack frequency is one episode per two-week period. In most cases, a family history of HAE is identified.

Disease severity of HAE is highly variable, including between patients and within families with the same mutation. There is no simple relationship between disease severity and C1-INH levels. Symptoms of HAE typically begin in childhood and worsen during puberty. In 75 percent of cases there is a family history of HAE. HAE has an autosomal dominant inheritance pattern.[5] In the cases with no family history, de novo mutations cause HAE and these mutations subsequently follow an autosomal dominant inheritance pattern. There are no known ethnic or gender differences in HAE rates.

Extremity attacks affect 96 percent of patients. These attacks are functionally disabling. If in the hands, patients have difficulty in driving, typing, and other uses of their hands. Attacks on the feet impede walking and standing. Extremity attacks interfere with work and school but rarely result in hospitalization. Abdominal attacks occur in 93 percent of patients with HAE. These result in mild-to-severe colicky pain and vomiting. Constipation or

Exhibit 3: Complement Testing in Recurrent Angioedema[6,11,12]

Type	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE Type 1	Low	Low	Low	Normal	Normal
HAE Type 2	Normal-high	Low	Low	Normal	Normal
HAE with normal C1-INH	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	Low	Low-normal	Low
ACE-I associated AE	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

diarrhea may occur. The attacks lead to functional intestinal obstruction and on examination the patient can have a protuberant abdomen, tenderness, and rebound. Fluid loss may lead to hemoconcentration and hypovolemic shock. Because the symptoms of an HAE abdominal attack mimic surgical emergencies, misdiagnosis and unnecessary surgery can occur. Laryngeal attacks occur in 50 to 60 percent of patients and are the most common cause of death in those with HAE.[8] These attacks require acute medication and airway management. In one survey there was a 40 percent incidence of asphyxiation in untreated laryngeal attacks.[9]

Common triggers for HAE attacks include emotional or physical stress, minor trauma, surgery, infections such as colds or influenza, ACE inhibitors, and changes in estrogen levels (oral contraceptives, hormone replacement therapy).[10] Unfortunately, many HAE episodes have no known trigger.

Diagnosis requires suspicion of HAE. It should be considered in a patient with recurrent episodes of angioedema without concomitant urticaria or unexplained abdominal pain. HAE should also be considered in those with a family history of angioedema or choking or throat swelling as a cause of sudden death. Diagnosis requires measurement of complement levels and C1-INH function and antigenic level, and if normal C1-INH, further genetic testing. Exhibit 3 compares complement results for several types of recurrent angioedema.[6,11,12] For those diagnosed with HAE, screening should be performed on all first-degree relatives.

The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization and disability, and prevent death and excessive pain. The three treatment strategies for HAE include on-demand medication to resolve angioedema symptoms as quickly as possible during an attack, short-term prophylaxis to prevent an attack when the patient will be exposed to a known trigger, and long-term prophylaxis to decrease the frequency and severity of ongoing attacks.[6, 11] All patients need on-demand treatment and many will also need long-term prophylaxis. Short-term prophylaxis should be prescribed for those with known triggers. Treatment for HAE must be individualized to provide optimal care and normalize health-related quality of life.

Plasma-derived (pd) and recombinant human (rh) C1-INH products are FDA approved for on-demand treatment of HAE attacks and supplement existing levels of C1-INH in Type 1 and 2 HAE. Both agents significantly reduce the time to symptom relief compared with placebo.[13,14] pdC1-INH is approved for adult and pediatric patients and rhC1-INH is approved for adult and adolescent patients.

Ecallantide is a plasma kallikrein inhibitor FDA approved for on-demand treatment of patients 12 years of age and older. The benefit of ecallantide is apparent within two hours after dosing and is maintained through 24 hours after dosing.[15] It is given as a subcutaneous injection but must be given by a healthcare professional because of the potential for anaphylaxis (3% to 4%).

Icatibant is a bradykinin B2 receptor antagonist FDA approved for on-demand treatment for adults 18 years of age and older.[16] Because this is self-administered subcutaneously and does not have the risk of anaphylaxis like ecallantide, it has become very commonly used. Because of icatibant, the majority of patients are now treating themselves at home rather than seeking care at an emergency room.[17]

Long-term prophylactic treatments of HAE include pdC1-INH, lanadelumab, and berotralstat. Subcutaneous pdC1-INH given twice a week reduces monthly HAE attacks by 95 percent compared to placebo.[18] Lanadelumab, a monoclonal antibody which binds plasma kallikrein and inhibits its proteolytic activity, was given as a subcutaneous injection every two weeks and reduced monthly attack rate by 87 percent compared to placebo.[19] Berotralstat is a once daily oral plasma kallikrein inhibitor approved for patients 12 years of age and

older which provides a significant reduction in attack rate (1.31 attacks per month; $p < .001$) relative to placebo (2.35 attacks per month).[20]

All patients should keep on-demand medication to treat two acute attacks at all times and treat all attacks as quickly as possible.[6,11] Short-term prophylaxis is administered when the patient knows they will experience known or potential triggers such as a surgical procedure requiring intubation. Short-term prophylaxis options include C1-INH concentrate, attenuated androgen therapy, or fresh frozen plasma. On-demand therapy should also be available at the surgical or dental procedure site. For long-term prophylaxis, first-line medications for HAE Types 1 and 2, include IV or subcutaneous C1-INH, berotralstat, and lanadelumab. For normal C1-INH HAE, tranexamic acid or progestin-only medication can be considered for prophylaxis. First-line medications for acute and prophylactic treatment are also used in children even if they are not necessarily FDA approved for that age group. For women with HAE, avoidance of estrogen use is advised. C1-INH replacement is recommended in pregnant and lactating women.

Patients should have an action plan for acute attacks and short-term prophylaxis. Long-term prophylaxis treatment options should be discussed with every patient for potential inclusion in a management plan. The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient.[6] Physicians should help patients optimize their treatment plan, coordinate care, and provide education about HAE.

Eight to 10 percent of the U.S. population has one of the 68,000 designated orphan diseases like HAE. This equates to 25 to 30 million individuals. Because so few people have a given disease, the cost of typical treatment for an orphan disease is expensive but treatment provides great benefits to affected individuals and families. The potential financial impact on managed care causes payers great concern due to perceived excess costs. These concerns result in barriers to treatment access including formulary exclusion, coinsurance, copayments, prior authorization, step therapy, and limits on quantity and resupply. In 2013, orphan disease medication expenditures were only 8.9 percent of total expenditures.[21] Additionally, orphan medication spending has been rising at a similar rate as all medication expenditures in the U.S. Overall, the costs of managing orphan diseases like HAE are in line with their incidence and are not increasing any faster than the costs for any other disease. Importantly, on-demand therapy and long-term prophylaxis treatment of HAE change the burden of illness significantly and have been shown to improve quality of life.[22,23]

There is still room for improvement in HAE treatment. Factors that will improve treatment are agents with increased efficacy and safety, reduced treatment burden, and improved accessibility. Innovations that may improve HAE patient outcomes include longer lasting prophylactic treatments, more targeted oral medications, additional monoclonal antibodies, RNA interference therapies, and gene therapies. Sebetralstat (oral plasma kallikrein inhibitor), PHVS416 (oral bradykinin receptor antagonist), garadacimab (Factor XIIa antagonist), donidalorsen (m-RNA anti-sense therapy which lowers prekallikrein production), and gene therapy are all under investigation for managing HAE and are showing good preliminary study results.

Conclusion

Whereas most cases of angioedema are mediated through mast cell mediators, HAE is mediated through bradykinin. Type 1 and 2 HAE result from a deficiency of C1-INH function. HAE normal C1-INH is likely bradykinin-mediated, but definitive diagnostic tests are lacking. Most treatments reduce bradykinin production or block a bradykinin receptor, which reduces vasodilation and swelling. HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, and patient quality of life. Clinicians need to consider HAE when encountering cases of angioedema. Costs of treatment for orphan diseases like HAE are not escalating faster than other drugs.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Multiple Sclerosis: Key Considerations in Managed Care Decision-Making

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Summary

Multiple sclerosis (MS) is a disabling neurodegenerative disease which can be treated with numerous agents to reduce relapses, improve symptoms, and slow disease progression. Additional new therapies and biomarkers are needed to address unmet needs in managing those with this disease.

Key Points

- Numerous disease-modifying treatment options are available for managing MS.
- Adherence and persistence with therapy are important to achieve value with MS treatment.
- There are still unmet needs in managing MS.
- Investigational BTK inhibitors may target an unmet need – progression independent of relapse activity (PIRA).

MULTIPLE SCLEROSIS (MS) IS AN IMMUNE-mediated, demyelinating disease, responsible for deleterious consequences within the central nervous system. There are almost one million people living with MS in the United States (U.S.). More people are being diagnosed with MS today than in the past, however, the reasons for this are not clear but there is no definitive evidence that the rate of MS is generally on the increase.[1] Likely contributors to increased diagnosis include greater awareness of the disease, better access to medical care, and improved diagnostic capabilities. Various epidemiologic studies have identified factors in the distribution of MS around the world that may eventually help determine what causes the disease. These factors include gender, genetics, age, geography, and ethnic background. For example, women are affected more commonly than men.

In terms of genetics, it has been known since the late 1800s that there is a familial occurrence for MS. Studies have shown that the risk of developing MS increases if an individual is related to someone that is afflicted with MS.[2,3] The closer related one is to the afflicted individual, the larger the risk. For the general population, there is only a 0.1 percent chance of developing MS in the Northern Hemisphere but the risk increases to approximately 1 percent if someone has a first cousin afflicted with MS. These numbers continue to rise in those with closer affected relatives. There is an estimated 1 to 2 percent risk for those with an uncle or aunt with MS, and 2 to 5 percent chance with a sibling, child, or parent with MS. If both parents have MS, then the risk jumps up to roughly 6 to 10 percent. In monozygotic twins, there is an approximate 25 to 30 percent risk of one twin developing MS if the other is affected.

Multiple sclerosis usually begins in early adulthood, between the ages of 20 and 40 years. Initial symptoms vary widely and affected individuals can experience one or more effects of nervous system

Exhibit 1: 2017 McDonald Criteria[10]

Number of clinical attacks*	Number of lesions with objective clinical evidence	Additional evidence required
≥ 2	≥ 2	None
≥ 2	1 plus good historical evidence	None
≥ 2	1	Dissemination in space by a further clinical episode at another site or by MRI.
1	≥ 2	Dissemination in time by a further clinical episode, by MRI or the presence of of CSF oligoclonal bands.
1	1	Dissemination in space by a further clinical episode at another site or by MRI. AND Dissemination in time by a further clinical episode, by MRI or the presence of of CSF oligoclonal bands.

* attacks should be separated by at least 30 days between onset

damage. Multiple sclerosis often causes sensory disturbances in the limbs, including paresthesia, numbness, pain, and itching. Problems with muscle control are common in people with multiple sclerosis. Affected individuals may have tremors, spasticity, hyperreflexia, weakness, or partial paralysis of the muscles of the limbs, difficulty walking, or poor bladder control. Multiple sclerosis is also associated with vision problems, such as blurred or double vision or partial or complete vision loss.

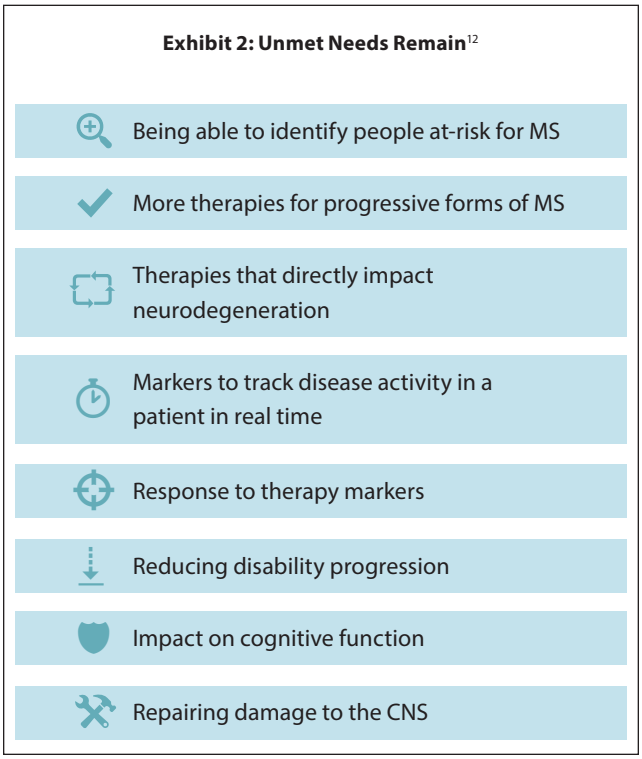
Progressive inflammation, demyelination of myelin sheaths, plaque formation, and axonal degeneration are the processes that characterize MS pathology. The inflammatory process in MS creates many targets for treatment.[4] Auto-reactive T lymphocytes and B cells attack myelin causing demyelination and axonal/neuronal injury. Irreversible axonal damage occurs from the onset of disease but is clinically silent until a threshold of axonal loss is exceeded. Inflammation predominates in the early phases of the disease.

T cells are activated by antigen presenting cells (APCs), which when activated, cross into the central nervous system (CNS) through a disrupted blood brain barrier (BBB).[5] Passage is facilitated by integrins, which are expressed by activated T cells, allowing the adhesion and passage of immune cells through the BBB. T-cell lymphocytes, specifically CD4+ (T-helper cells) and CD8+ (cytotoxic T cells), recognize myelin as foreign and attack it, initiating a damaging, inflammatory response. T-helper (Th) type cell subtypes also secrete proinflammatory cytokines such as interleukin-17. CD8+ cells kill neuroglial cells, expose axons, and activate oligodendrocyte death.

CNS lesions in MS patients contain B cells, plasma cells and antibodies.[6] B cells become activated and an influx of macrophages, eosinophils, and neutrophils occur. Antigen-activated B cells differentiate into antibody-secreting plasma cells, serve as APCs to T cells, and secrete inflammatory cytokines. Infiltrating B cells and myelin antibodies also activate complement, which promotes inflammation during acute phases and is neuroprotective during periods of relapse. Several of the disease-modifying therapies for MS target T and B cells.

The brain microglia have now been recognized as important in the pathology of MS. Microglia are resident cells of the brain that regulate brain development, maintenance of neuronal networks, and injury repair.[7] Microglia serve as brain macrophages but are distinct from other tissue macrophages owing to their unique homeostatic phenotype and tight regulation by the CNS microenvironment. They are responsible for the elimination of microbes, dead cells, redundant synapses, protein aggregates, and other particulate and soluble antigens that may endanger the CNS. Active MS lesions are characterized by diffuse infiltration with microglia in addition to peripheral macrophages, T and B cells,

Exhibit 2: Unmet Needs Remain[12]



and plasma cells. Microglia are present in all stages of lesion formation as a driver of inflammation and are detectable in slowly expanding lesions linked to disease progression.[8] Therapies to target microglia are being developed.

Four disease courses have been identified in multiple sclerosis – clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).[9] CIS is the very first episode of MS symptoms. RRMS with episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery and no apparent progression of disease is the most common type of MS.

MS is diagnosed based on clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and spinal cord and cerebrospinal fluid examination. Clinically, symptoms of an attack must be compatible with the pattern of neurologic deficits seen in MS, which typically means that the duration of deficit is days to weeks. Traditionally, MS could not be diagnosed after only a single symptomatic episode, as diagnosis required repeat attacks suggesting the appearance of lesions separated in time and space. In the past, treating physicians were content to "sit back and watch" after a single episode, as it was assumed the disease would "declare" itself. The 2017 McDonald criteria allow diagnosis of MS even with a first clinical episode (Exhibit 1).[10] Early diagnosis is important because there is growing evidence that early intervention during the inflammatory phase of the disease is useful in slowing disability.

The five main treatment goals in MS are modifying or reducing relapses, delaying progression to disability, treating relapses, managing symptoms, and maintaining an acceptable quality of life.[11] A sixth goal is inspiring hope for the future. This is a critical component of patient education, as it can energize patients with MS and make healthy coping more feasible.

There are now 19 different medications available for treating MS. All are approved for RRMS; ocrelizumab is an option for PPMS and three agents are approved for active SPMS. All the FDA-approved therapies reduce annual relapse rate, accumulation of disability, and MRI evidence of disease in RRMS but their potencies, safety, and tolerability vary.

The sphingosine 1-phosphate (S1P) receptor modulators class is one area of significant treatment expansion with four available agents. This class is given orally and appears more effective than older oral medications such as teriflunomide and dimethyl fumarate. S1P regulates diverse cellular responses involved in immunity, heart rate, smooth muscle tone, and endothelial barrier function. Subtype 1 S1P receptors (S1P1) are expressed on the surfaces of lymphocytes and are important in regulating egression from lymph nodes. In MS, the S1P receptor modulators indirectly antagonize the S1P1 receptor's function and sequester lymphocytes in lymph nodes resulting in the depletion from the circulation and hence immunosuppression.[12] Fingolimod was the first S1P agent approved in the U.S. in 2010 for RRMS. The newer generation agents, unlike fingolimod, are more selective and thus cause lower rates of off-target events (including bradycardia and atrioventricular block). The selective S1P agents have the advantage of shorter half-lives and more rapid lymphocyte recovery post discontinuation. All four S1P receptor modulators are FDA approved for RRMS and all but fingolimod for active SPMS. The three newer agents have all been shown to be disease-modifying with reduced CNS lesions, annualized relapse rate, and brain volume loss but they have not been directly compared to each other.[12] There are numerous fingolimod generics available.

Despite considerable progress with disease-modifying therapies reducing inflammation and attack rates, there are several unmet needs in MS treatment. Exhibit 2 illustrates several of these.[13] It is very important to also identify what patients and caregivers perceive to be important needs. In one survey, several were identified. These include a desire

to play a more active role in treatment, more sources of disease information, more active role in rehabilitation issues, better understanding of the social impact of MS, and improved psychological support.[14]

Bruton's tyrosine kinase (BTK) inhibitors are a likely future advance in MS treatment, targeting the unmet need of disability accumulation that can occur despite relapse control. This class, which is already approved for use in hematological and neoplastic disorders, is being investigated in MS and is involved in microglia activation. Chronically activated microglia have been associated with focal smoldering pathology known as slowly expanding lesions (SELs) which led to progression independent of relapse activity (PIRA). In contrast to active demyelinating lesions, the pathology of SELs is characterized by a low degree of inflammation and with T and B cells at the lesion core surrounded by a dense network of activated iron-laden microglia and peripheral macrophages.[15,16] SELs with paramagnetic rims of activated microglia at their edges contribute to the failure of remyelination, resulting in further destruction of the surrounding areas. To date, MS disease-modifying therapies have little if any effect on microglia activation within the CNS.

The possibility of BTK inhibitors in MS treatment is exciting because these agents can more easily cross the BBB than many MS drugs and can affect a wide variety of immune cells, including B cells, natural killer cells, and microglia, which all play major roles in MS inflammation and evidence suggesting that progressive MS is driven by cells from within the CNS such as microglia and astrocytes rather than peripheral immune cells.

Five BTK inhibitors (evobrutinib, tolebrutinib, fenebrutinib, remibrutinib, and orelabrutinib) are being studied for the treatment of patients with MS. All but orelabrutinib have shown promising results in Phase II trials and have moved to Phase III. The Phase II orelabrutinib trial is due to be completed in 2024. There have been some struggles with the Phase III trials. Evobrutinib did not meet its primary end points of reducing relapse in the Phase III EVOLUTION trials.[17] Also because of possible drug induced liver injury, the FDA has placed further patient enrollment holds on clinical trials of fenebrutinib, evobrutinib, orelabrutinib, and tolebrutinib.[17-20]

Payers have a particular focus on MS treatment because it is a very costly chronic disease, with direct costs of prescription drugs and indirect costs as significant cost drivers.[21] Compared with healthy individuals, patients with MS are more likely to utilize healthcare services. Newly diagnosed patients are 3.5 times more likely to be hospitalized, twice as likely to have one or more emergency department visits, and 2.4 times more likely to have one or more visits for physical, speech, or occupational therapy. Meta-analyses have shown that MS ranked second behind heart failure in direct all-cause medical costs for chronic conditions. The total lifetime cost per patient with MS is estimated to be $4.1 million (in 2010 dollars). For patients using disease-modifying therapy to manage their MS, approximately 75 percent of total MS-related healthcare costs is for these agents.[22] Additionally, as disability progresses, the overall healthcare costs increase.

In the past, payers managed MS drugs under the pharmacy or medical benefit depending on mode and site of administration. By 2023, many payers have changed the way they are managing medications covered under the medical benefit, by implementing prior authorization (PA) and other utilization management approaches traditionally associated with pharmacy benefit management.[23] Other payers have moved agents for the treatment of MS (including orals) to specialty pharmacy distribution, allowing far more control over tracking and utilization management.

There is currently insufficient Class I evidence for a detailed MS treatment algorithm because there are few comparative trials and virtually no comparative trials of later generation agents. The lack of definitive clinical evidence to guide MS treatment decisions has become increasingly important as the number of therapeutic options continues to increase annually. Payers struggle with which drug is right for which patient while balancing cost, outcomes, and access.

Payers contend that the lack of universally acceptable clinical practice guidelines has hindered their ability to develop consistent prior authorization criteria acceptable to the neurology community. In the absence of consensus, payers are forced to use product labeling for their criteria. However, product labeling is normally based on clinical trial data, and the efficacy measurement criteria used in clinical trials often differs from the criteria used in clinical practice.

Payers would consider revising their utilization management criteria if the neurology community agreed on consensus guidelines that were appropriately vetted.

No matter what medication is chosen for a given patient, adherence with that medication is vital for achieving optimal outcomes. Payers make a large investment in MS treatments but adherence and persistence to therapy in MS (like all chronic diseases) can be an issue. Some of the reasons cited by patients with MS for stopping a medication include not feeling any better, adverse events are worse than the

disease, an exacerbation occurred despite medication, insurance stopped covering the medication, no longer afford the medication co-payments, and the hope that something else would work better.[24]

Factors that can influence adherence and persistence to disease-modifying therapies include medication tolerability, patient physical and cognitive decline, frequency and complexity of the dosing regimen, duration of disease and treatment, patient perceptions of medication benefits and risks, and economic burden associated with medication. Interventions aimed at optimizing medication adherence and persistence need to incorporate new and creative approaches that take individual patient needs and lifestyle into account. When considering a disease-modifying therapy, it is important to evaluate the safety and tolerability profile of the medication, the individual patient's needs and lifestyle, and how the specific requirements and characteristics of the medication intersect with the patient's characteristics.[25]

Beyond improving adherence and persistence with therapy, payers would like biomarkers for MS. Establishing satisfactory biomarkers for MS has proven to be very difficult, due to the clinical and pathophysiological complexities of the disease. Potential new biomarkers are divided into three subgroups – genetic-immunogenetic, laboratory, and imaging. The ultimate goal would be better predictors for prognosis, medication selection, disability progression, and adverse event prediction.

Conclusion

There are now numerous disease-modifying treatment options for managing MS. Adherence and persistence with therapy is important for achieving value with MS treatment. There are still several unmet needs in MS treatment. One of these, PIRA, may be targeted in the future with new therapies including BTK inhibitors.

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MEDICAL DIRECTORS, PHYSICIANS, NURSES, ADMINISTRATORS, and OTHER HEALTHCARE PROFESSIONALS

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Contact Jeremy Williams at jwilliams@namcp.org for more information.